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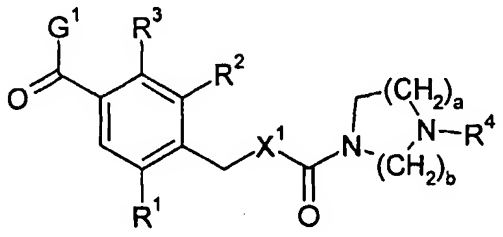
(54) Title: DIAZACYCLOALKANES AS OXYTOCIN AGONISTS



(1)

(57) Abstract: Compounds according to general formula (1), wherein G^1 is NR^5R^6 or a fused polycyclic group are novel. They are selective and potent oxytocin agonists. Pharmaceutical compositions of such compounds are useful in the treatment of, *inter alia*, erectile dysfunction.

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DIAZACYCLOALKANES AS OXYTOCIN AGONISTS

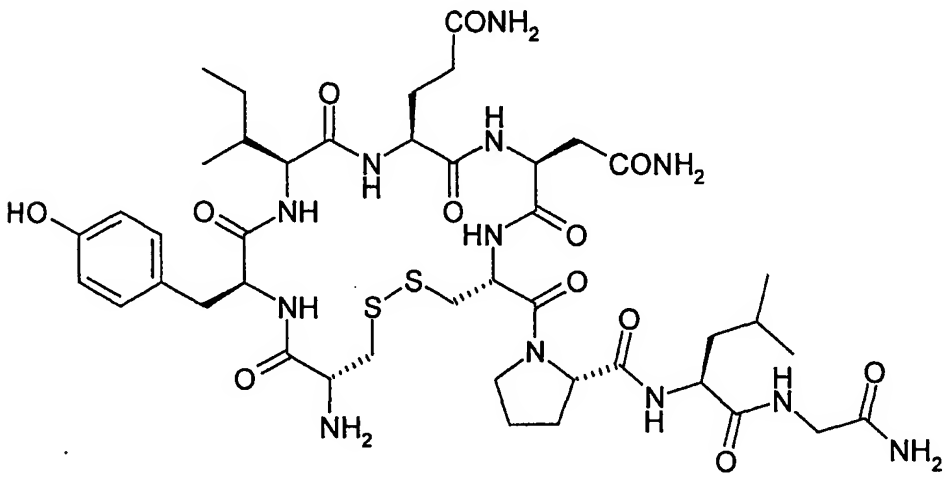
FIELD OF THE INVENTION

The present invention relates to a series of non-peptide oxytocin agonists and to pharmaceutical compositions comprising such compounds. The compositions are useful for the treatment of certain physiological disorders, such as erectile dysfunction.

BACKGROUND

Neurophyseal hormones

The neurophyseal hormones oxytocin (OT) and vasopressin (VP) are cyclic nonapeptides secreted by the posterior pituitary gland. The structure of oxytocin is shown below.



Oxytocin – *cyclo*^{1,6}-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2

Vasopressin differs from oxytocin in that it has phenylalanine at position 3 in place of isoleucine and arginine at position 8 in place of leucine. Both hormones are synthesised *in vivo* as larger precursors, neurophysins, which are subject to post-translational processing to release the mature peptides. OT and VP act through a family of heptahelical receptors.

The first target organs to be identified for OT were the uterus, where it is implicated in the onset and progress of labour, and mammary glands, where it is involved in the regulation of milk expression. Other organs also express OT receptors, and it is clear that OT has a range of physiological roles that have not been fully elaborated yet. In particular, it has been suggested that OT acting in the CNS is involved in the erectile response in males, and in the regulation of female sexual arousal. For example, OT is erectogenic when administered *i.c.v.* to male rats. It also has erectogenic activity when given *i.v.*, but the doses required are up to two orders of magnitude greater, which is consistent with a central mode of action.

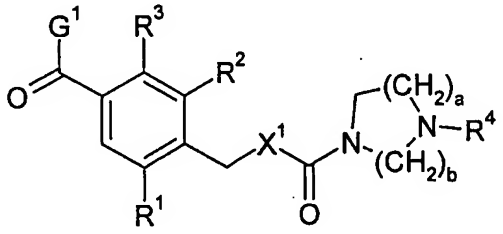
Oxytocin agonists and antagonists

A number of peptide analogues of OT are known in the literature. These include both agonists and antagonists. OT and its agonists are used, for example, to accelerate labour and to increase uterine muscle tone to control post-partum bleeding, and one antagonist, atosiban, has recently been registered as a treatment for pre-term labour. However, the peptidic nature of these compounds means that they are not likely to be bioavailable after oral dosing or to cross efficiently into the CNS. In order to get drugs that can be given orally and to be able to exploit the central effects of OT, attention has increasingly turned to non-peptides. As a result, there are many publications describing non-peptide OT antagonists in early-stage development. So far, however, there have been no reports of non-peptide OT agonists. This is not unexpected, as it is generally held that it is easier to find a receptor antagonist than an agonist.

So there remains a need for non-peptide OT receptor agonists. Such compounds should preferably be selective for the OT receptor over the VP receptors. They could be expected to show therapeutic utility in male and female sexual dysfunction, particularly male erectile dysfunction, in promoting labour, in controlling post-partum bleeding, in increasing milk let-down as well as a number of other indications.

SUMMARY OF THE INVENTION

We describe herein a series of potent and specific OT receptor agonists. In a first aspect, the present invention comprises novel compounds according to general formula **1**, and pharmaceutically acceptable salts thereof.



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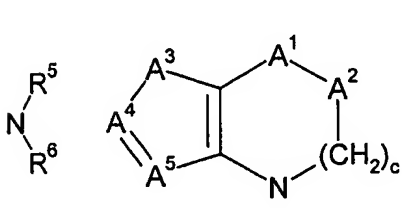
G^1 is a group according to general formula **2**, **3**, **4**, **5**, **6** or **7**.



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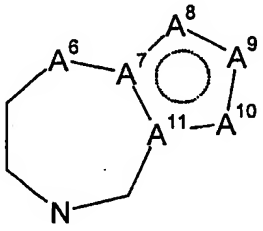

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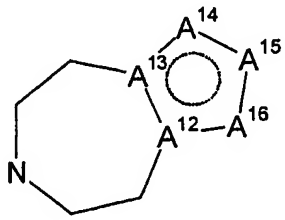

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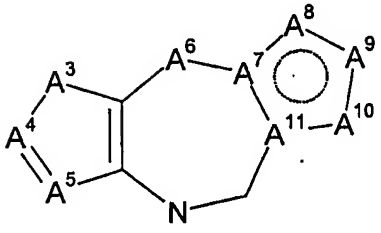

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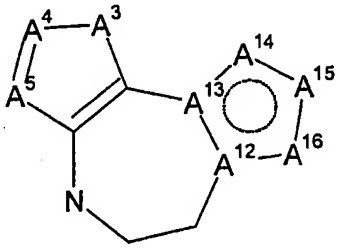

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A^1 is CH_2, CH(OH), NH, N–alkyl, O or S; A^2 is CH_2, CH(OH), C(=O) or NH; A^3 is S, NH, N–alkyl, –CH=CH– or –CH=N–; A^4 and A^5 are each CH or N; A^6 is CH_2, NH, N–alkyl or O; A^7 and A^{11} are C or N; A^8 and A^9 are CH, N, NH, $N(CH_2)_dR^7$ or S; A^{10} is –CH=CH–, CH, N, NH, N–$(CH_2)_d$–R^7 or S; A^{12} and A^{13} are N or C and A^{14}, A^{15} and A^{16} are NH, N–CH_3, S, N or CH, provided that not more than one of A^8, A^9 and A^{10} is NH, N–$(CH_2)_d$–R^7 or S; that A^7 and A^{11} are not both simultaneously N; that neither A^7 nor A^{11} is N if one of A^8, A^9 and A^{10} is NH, N–$(CH_2)_d$–R^7 or S; that if A^{10} is –CH=CH– then A^8 is N, A^9 is CH and both A^7 and A^{11} are C; that if A^{10} is not –CH=CH– then one of A^8, A^9 and A^{10} is NH, N–$(CH_2)_d$–R^7 or S

or one of A^7 and A^{11} is N; that not more than one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S; that A^{12} and A^{13} are not both simultaneously N; that if one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S then A^{12} and A^{13} are both C; and that one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S or one of A^{12} and A^{13} is N.

X^1 is O or NH.

R^1, R^2 and R^3 are each H, alkyl, O–alkyl, F, Cl or Br.

R^4 is H, alkyl, optionally substituted phenyl, pyridyl, thienyl or furyl, or is $-(CH_2)_e-R^8$.

R^5 and R^6 are each independently alkyl, Ar or $-(CH_2)_f-Ar$, where Ar is optionally substituted phenyl or thienyl.

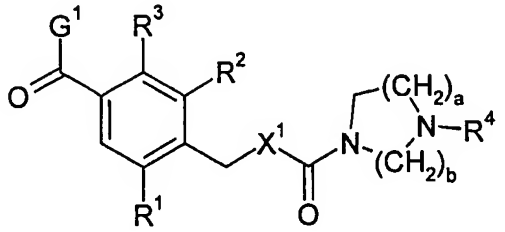
R^7 and R^8 are each independently H, alkyl, optionally substituted phenyl, pyridyl, thienyl or furyl, F, OH, O–alkyl, S-alkyl, O-acyl, NH_2, NH–alkyl, $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2–alkyl, $CONH_2$, CONH–alkyl, $CON(alkyl)_2$, CN or CF_3.

a is 1 or 2, b is 1, 2 or 3, c is 1 or 2, d is 1, 2 or 3; e is 1, 2 or 3 and f is 1, 2 or 3.

In a second aspect, the present invention comprises pharmaceutical compositions of these novel compounds, which compositions are useful for the treatment of, *inter alia*, male erectile dysfunction. In further aspects, the present invention comprises the use of such compositions in therapy and therapeutic methods using the compositions.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention comprises novel benzyl carbamates and ureas according to general formula **1**.



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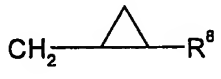
In this general formula the substituents R^1, R^2 and R^3 are independently selected from hydrogen (H), alkyl groups, alkoxy (O–alkyl) groups, and the halogens fluorine (F), chlorine (Cl) and bromine (Br). Preferably, at least one of R^1, R^2 and R^3 is H and at least one is not H. More preferably, one of R^1, R^2 and R^3 is an alkyl group or a halogen and the others are H. Most preferably, R^1 is methyl or Cl and R^2 and R^3 are both H.

The linking group X^1 is selected from oxygen (O) and unsubstituted nitrogen (NH). Preferably, X^1 is NH.

The integer a may be 1 or 2, and the integer b may be 1, 2 or 3. Preferably a is 1 and b is 2 such that this ring is a piperazine.

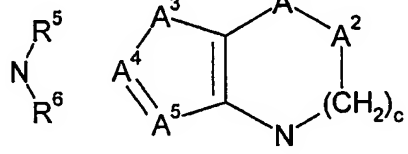
The substituent R^4 is selected from H, alkyl groups, optionally substituted phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl groups, a group-(CO)-O–$(CH_2)_eR^8$ where e is 1, 2, 3 or 4, a group –$(CH_2)_eR^8$, where e is 1, 2, 3 or 4, -CH_2-CH=CH-CH_2-R^8, -CH_2-C≡C-CH_2-R^8, -$(CH_2)_g$-CH(OH)-$(CH_2)_h$-R^8, where g and h are independently 1 or 2,

-$(CH_2)_i$-O-$(CH_2)_j$-R^8 where i and j are independently 1 or 2,and 

R^8 is selected from H, F, CF_3, alkyl groups, O-alkyl groups, S-alkyl groups, O-acyl groups, hydroxyalkyl groups, amino groups such as NH_2, NH-alkyl, N(alkyl)$_2$, 1-pyrrolidinyl, 1-piperidinyl and 4-morpholinyl, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CN and optionally substituted phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl groups. Suitable optional substituents for the phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl groups in R^4 and R^8 include F, Cl, Br, CF_3,

alkyl groups, OH, O-alkyl groups, hydroxyalkyl groups, amino groups such as NH_2, NH-alkyl and $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$, oxadiazolyl, thiadiazolyl, CN and NO_2. The phenyl, pyridyl, thienyl furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl group may have up to three such substituents which may be the same or different.

The group G^1 is a disubstituted nitrogen such that the C(=O)–G^1 bond is an amide bond. G^1 is selected from an acyclic group according to general formula **2**, a fused bicyclic group according to general formulae **3**, **4** and **5**, and a fused tricyclic group according to general formulae **6** and **7**,



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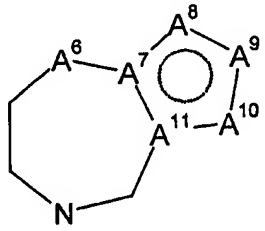

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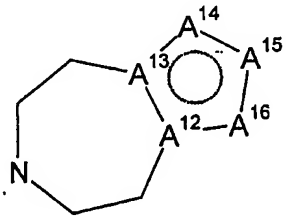

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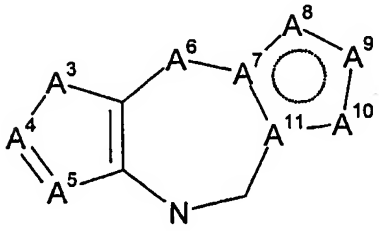

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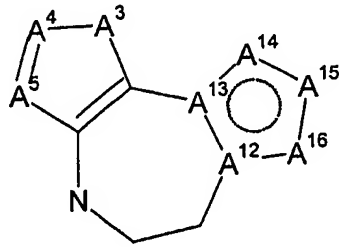


7

In general formula **2**, R^5 and R^6 are independently selected from alkyl, Ar and $-(CH_2)_f$–Ar, where f is 1, 2 or 3 and Ar is selected from thienyl and optionally substituted phenyl. Suitable substituents for the phenyl group are alkyl groups, OH, alkoxy groups, halogens, NH_2, NH–alkyl and $N(alkyl)_2$. The phenyl group may be substituted with up to three such substituents which may be the same or different.

In general formula **3**, A^1 is selected from CH_2, CH(OH), NH, N–alkyl, O and S. A^2 is selected from CH_2, CH(OH), C(=O) and NH, and c is 1 or 2, preferably 2. It is preferred that when A^2 is NH then A^1 is CH_2. It is also preferred that when A^2 is C(=O) then A^1 is NH or N–alkyl.

In general formulae **3**, **6** and **7**, A^3 is selected from S, NH, N–alkyl, –CH=CH– and –CH=N– and A^4 and A^5 are each selected from CH and N. In a preferred embodiment, A^3 is S and A^4 and A^5 are both CH, so as to form a thiophene ring. In another preferred embodiment, A^3 is –CH=CH– and A^4 and A^5 are both CH, so as to form a benzene ring. In another preferred embodiment, A^3 is –CH=N– and A^4 and A^5 are both CH, so as to form a pyridine ring. In another preferred embodiment, A^3 is –CH=CH–, A^4 is CH and A^5 is N, again so as to form a pyridine ring.

In general formulae **4** and **6**, A^6 is selected from CH_2, NH, N–alkyl and O, A^7 and A^{11} are selected from C and N, A^8 and A^9 are selected from CH, N, NH, N–$(CH_2)_d$–R^7 and S and A^{10} is selected from –CH=CH–, CH, N, NH, N–$(CH_2)_d$–R^7 and S, where d is 1, 2 or 3 and R^7 is selected from H, F, CF_3, alkyl groups, OH, O-alkyl groups, S-alkyl groups, O-acyl groups, amino groups such as NH_2, NH-alkyl and N(alkyl)$_2$, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CN and optionally substituted phenyl groups. Suitable optional substituents for the phenyl groups in R^7 include F, Cl, Br, CF_3, alkyl groups, O-alkyl groups, amino groups such as NH_2, NH-alkyl and N(alkyl)$_2$, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, CN and NO_2. The phenyl group may have up to three such substituents which may be the same or different.

The ring constituted by A^7, A^8, A^9, A^{10} and A^{11} is aromatic, and accordingly the groups must satisfy certain requirements. When A^{10} is –CH=CH– the ring is a six-membered ring. As such, it can only comprise atoms of the type –C(R)= and –N=. Hence A^7 and A^{11} must both be C and A^8 and A^9 must be either CH or N. We have found that suitable activity is only obtained when A^8 is N and A^9 is CH. When A^{10} is not –CH=CH– then the ring is a five-membered ring. In this case one, and only one, of the atoms in the ring must be S or a trigonal nitrogen. In this context, a "trigonal nitrogen" is a nitrogen atom linked covalently to three different atoms. Two of these atoms are the immediate neighbours to the nitrogen atom in the five-membered ring. The third is a hydrogen, carbon or other atom linked to the five-membered ring. Thus it follows that, when A^{10} is not –CH=CH– then one (and only one) of A^7, A^8, A^9, A^{10} and A^{11} must be S or a trigonal nitrogen. Hence the selection of A^7, A^8, A^9, A^{10} and A^{11} is subject to the following restrictions.

1) If A^{10} is not –CH=CH– then one of A^8, A^9 and A^{10} is NH, N–$(CH_2)_d$–R^7 or S or one of A^7 and A^{11} is N.

2) Not more than one of A^8, A^9 and A^{10} may be NH, N–$(CH_2)_d$–R^7 or S.
3) A^7 and A^{11} may not both simultaneously be N.
4) Neither A^7 nor A^{11} may be N if one of A^8, A^9 and A^{10} is NH, N$(CH_2)_dR^7$ or S.

In a preferred embodiment, A^6 is NH. In another preferred embodiment, A^8 is NH or N–$(CH_2)_d$–R^7. In a more preferred embodiment, A^8 is NH or N–$(CH_2)_d$–R^7, A^9 is N and A^{10} is CH.

In general formulae **5** and **7**, A^{12} and A^{13} are selected from N and C and A^{14}, A^{15} and A^{16} are selected from NH, N–CH_3, S, N and CH. Again, these atoms constitute an aromatic five-membered ring and so there must be one, and only one, S or trigonal nitrogen. Hence the selection of A^{12}, A^{13}, A^{14}, A^{15} and A^{16} is subject to the following restrictions.

1) One of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S or one of A^{12} and A^{13} is N.
2) Not more than one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S.
3) A^{12} and A^{13} may not both simultaneously be N.
4) If one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S then A^{12} and A^{13} are both C

As used herein, the term "alkyl" is intended to designate lower alkyl groups, i.e. saturated hydrocarbon groups of between one and six carbon atoms, including linear, branched and cyclic alkyl groups. Examples of "alkyl" include, but are not limited to: C_1 - methyl, C_2 - ethyl, C_3 - propyl, isopropyl, cyclopropyl, C_4 - n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, cyclopropylmethyl, methylcyclopropyl, C_5 – n-pentyl, neopentyl, cyclopropylethyl, dimethylcyclopropyl, and C_6 – n-hexyl, cyclohexyl, bicyclo[3.1.0]hexyl.

The term "alkenyl" denotes a lower alkenyl group, i.e. a mono-unsaturated hydrocarbon group of between two and six carbon atoms, including linear, branched and cyclic alkenyl groups. Examples of "alkenyl" include, but are not limited to: C_2 - vinyl, C_3 - allyl, 1-methylvinyl, 1-propenyl, C_4 – but-3-enyl, but-2-enyl, methallyl.

The term "alkynyl" denotes a lower alkynyl group, i.e. an unsaturated hydrocarbon group of between two and six carbon atoms which includes a carbon-carbon triple bond, including linear, branched and cyclic alkynyl groups. Examples of "alkynyl" include, but are not limited to: C_2 - ethynyl, C_3 - propargyl, 1-propynyl.

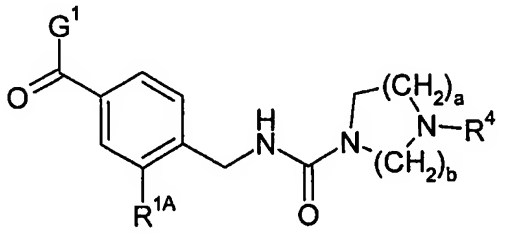
The term "hydroxyalkyl" denotes an alkyl group as defined above in which one or more of the hydrogen atoms are replaced by hydroxyl groups (OH). In general, not more than one hydroxyl group will be attached to any particular carbon atom within the hydroxalkyl group. Examples of hydroxyalkyl groups include, but are not limited to: hydroxymethyl ($HOCH_2$), 1-hydroxyethyl ($CH_3CH(OH)$), 2-hydroxyethyl ($HOCH_2CH_2$), 1,2-dihydroxyethyl ($HOCH_2CH(OH)$) 4-hydroxy-2-pentyl ($CH_3CH(OH)CH_2CH(CH_3)$), and 4-hydroxy-cyclohexyl.

The term "acyl" denotes a group R-C(=O), where R is H, a saturated or unsaturated hydrocarbon moiety of up to seven carbon atoms or a pyridyl or thienyl group. Examples of acyl groups include, but are not limited to: formyl, acetyl, pivaloyl, benzoyl and nicotinoyl.

The compounds according to the present invention generally contain a basic nitrogen atom and so are capable of forming addition salts with protic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, benzoic acid, maleic acid, citric acid, fumaric acid, methanesulphonic acid and the like. The compounds of the present invention may also contain an acidic group, such as a carboxylic acid group at R^7 or R^8 These compounds may exist as inner salts (zwitterions) or as salts such as sodium, potassium, magnesium, calcium or tetra-alkylammonium salts. To the extent that such salts are pharmaceutically acceptable, they are included within the scope of the present invention.

The compounds according to the present invention may have one or more stereogenic centres ("asymmetric carbon atoms") and so may exhibit optical isomerism. The scope of the present invention includes all epimers, enantiomers and diastereomers of compounds according to general formula **1**, including single isomers, mixtures and racemates.

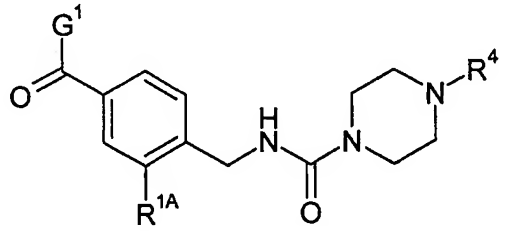
Particularly preferred embodiments within the present invention are those compounds that combine two or more of the preferred features described above. One such particularly preferred embodiment is a urea according to general formula **8**.



8

In general formula **8**, R^{1A} is methyl or Cl. G^1, R^4, a and b are as previously defined.

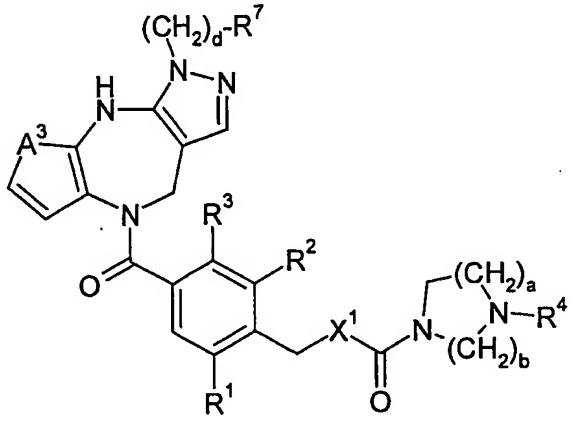
More preferred is a urea according to general formula **9**.



9

In general formula **9**, R^{1A}, R^4 and G^1 are as previously defined.

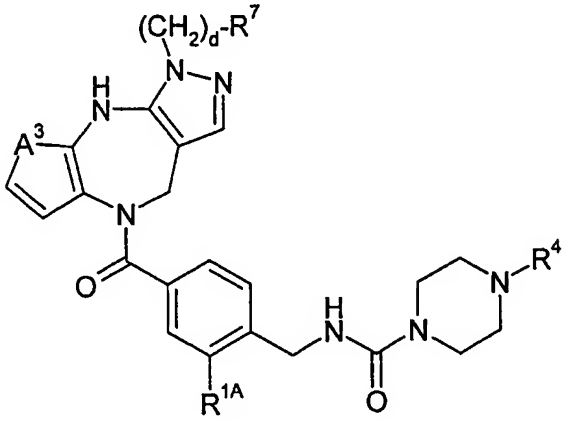
Another particularly preferred embodiment is a compound according to general formula **10**, which corresponds to a compound according to general formula **1** in which G^1 is a group according to general formula **6** wherein A^4, $A^5$and A^{10} are all CH, A^6 is NH, A^7 and A^{11} are both C, A^8 is $N(CH_2)_dR^7$ and A^9 is N.



10

In general formula **10**, R^1, R^2, R^3, R^4, R^7, A^3, X^1, a, b and d are as previously defined.

A most preferred embodiment is a compound according to general formula **11**.



11

In general formula **11**, R^{1A}, R^4, R^7, A^3 and d are as previously defined.

Individual preferred compounds within the invention include:

5-(4-(4-cyclopropylmethylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-benzylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(3-hydroxybenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(3-hydroxymethylbenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

1-methyl-5-(3-methyl-4-(4-(4-picolyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

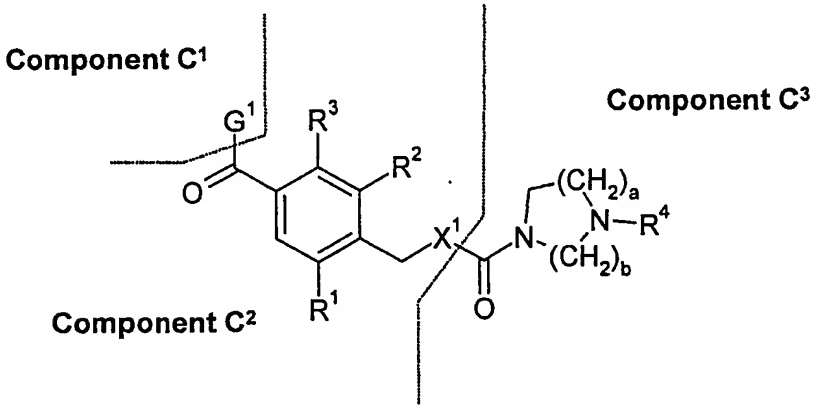
1-methyl-5-(3-methyl-4-(4-(3-(methylthio)propyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(2-aminoethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine, and

5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine.

The compounds of the present invention can be prepared by standard chemical manipulations. In general, compounds according to general formula **1** can be considered to consist of three component parts:

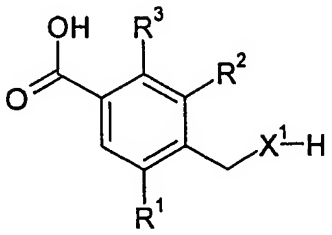
- Component C^1 corresponding to G^1
- Component C^2 corresponding to the substituted benzoyl unit
- Component C^3 corresponding to the saturated heterocycle



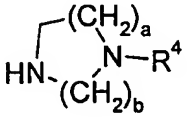
Intermediates corresponding to these components are prepared and then assembled to give the final product. These three components are:

(i) for C^1, a secondary amine G^1–H

(ii) for C^2, a substituted benzoic acid



(iii) for C^3, a monosubstituted saturated heterocycle

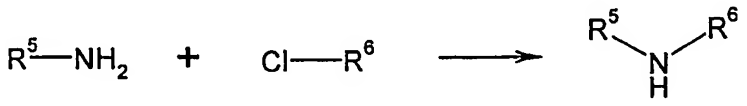


It will be recognised that the substituted benzoic acid that serves for C^2 has two functional groups, one of which will need temporary protection during the assembly of the final compound. The principles of functional group protection are well known in the art and are described in, for example, J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, 1973; T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd edition, John Wiley, 1991; and P.J. Kocienski, "Protecting groups", Georg Thieme Verlag, 1994. The carboxylic acid group will usually be protected as an ester, such as the methyl, benzyl or tert-butyl ester. The primary amine of the benzoic acid (when X^1 = NH) will usually be protected as a carbamate derivative such as the *tert*-butyl carbamate (BOC derivative), the benzyl carbamate (CBZ or more simply Z derivative) or the 9-fluorenylmethyl carbamate (Fmoc derivative). When X^1 = O the resulting alcohol function will usually be protected as an ester such as an acetate, or an ether such as a methoxymethyl, tetrahydropyranyl or trialkylsilyl ether. Other functional groups may require protection. For example, the group G^1 may include one or more primary or secondary amino groups which may need protection. In the following general description of the synthetic methodology it will be assumed that such protection is used when necessary.

(i) Preparation of secondary amine for C^1

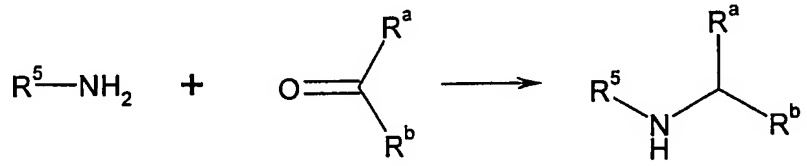
Acyclic secondary amines corresponding to HNR^5R^5 are well known. Many are items of commerce. Those that are not may be prepared according to published methods or by simple modification of such methods. Some particularly useful methods are listed below.

a) Alkylation



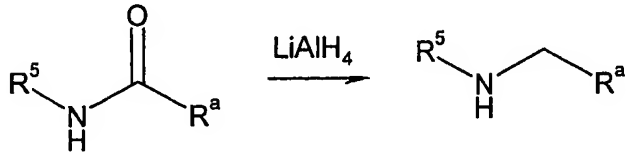
(This method is only applicable in cases where further alkylation can be avoided.)

b) Reductive amination



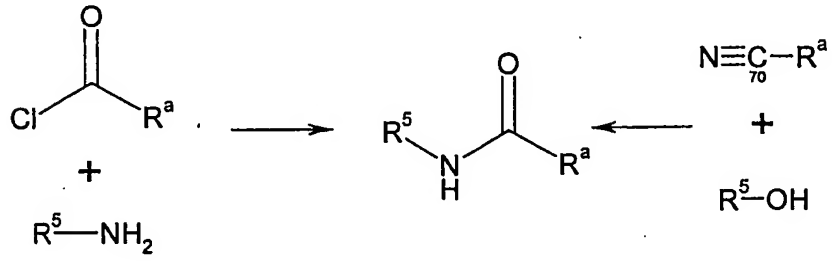
(where R^aCHR^b corresponds to R^6)

c) Amide reduction



(where R^aCH_2 corresponds to R^6)

The starting amide can itself be prepared using well known methods.



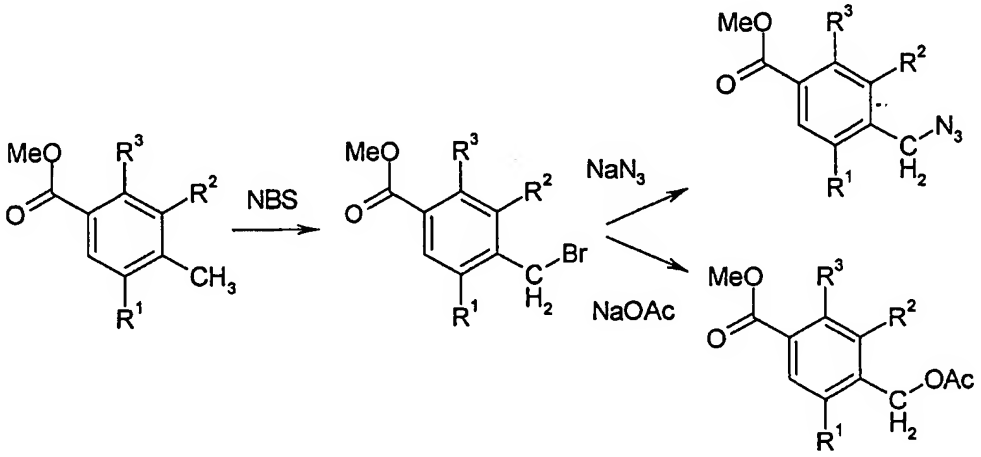
Secondary amines corresponding to C^1 where G^{11} is a group according to general formulae **3 – 7** are generally not commercially available. They can be prepared according to published methods, or by obvious modifications of such methods. Particularly useful methods are described in: Aranapakam *et al.*, Bioorg. Med. Chem. Lett. 1993, 1733; Artico *et al.*, Farmaco. Ed. Sci. 24, 1969, 276; Artico *et al.*, Farmaco. Ed. Sci. 32, 1977, 339; Chakrabarti *et al.*, J. Med. Chem. 23, 1980, 878; Chakrabarti *et al.*, J. Med. Chem. 23, 1980, 884; Chakrabarti *et al.*, J. Med. Chem. 32, 1989, 2573; Chimirri *et al.*, Heterocycles 36, 1993, 601; Grunewald *et al.*, J. Med. Chem. 39, 1996, 3539; Klunder *et al.*, J. Med. Chem. 35, 1992, 1887; Liegéois *et al.*, J. Med. Chem. 37, 1994, 519; Olagbemiro *et al.*, J. Het. Chem. 19, 1982, 1501; Wright *et al.*, J. Med. Chem.

23, 1980, 462; Yamamoto *et al.*, Tet. Lett. 24, 1983, 4711; and International patent application, publication number WO99/06403.

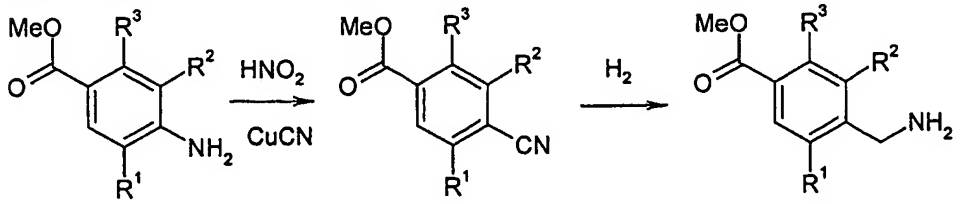
(ii) Preparation of substituted benzoic acid for C^2

Substituted benzoic acids corresponding to C^2 are not generally items of commerce, but they can be prepared using published methods or obvious variations of such methods. The main challenge is generally the elaboration of the $-CH_2X^1H$ functionality at the 4-position. Some useful transformations are listed below.

a) Bromination/Substitution



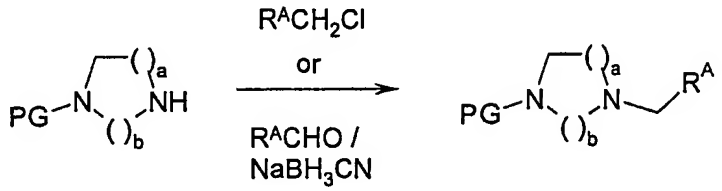
b) Sandmeyer reaction/reduction



(iii) Preparation of heterocycle derivative for C^3

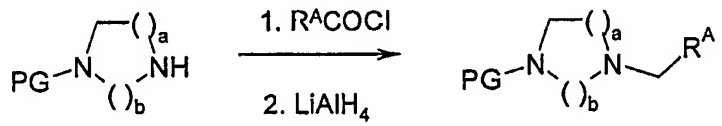
Certain heterocycles corresponding to C^3, particularly *N*-aryl piperazines, are items of commerce. Other heterocycles can be prepared according to the methods described in the literature. Useful transformations include the following.

a) Alkylation or reductive alkylation

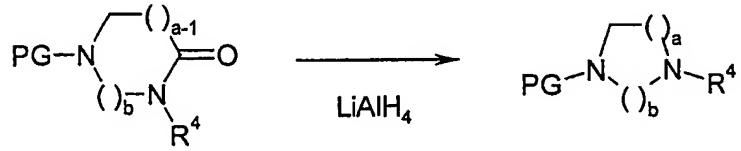


(where PG is a protecting group and R^ACH_2 is R^4)

b) Acylation/reduction



c) Reduction



With the three components, suitably protected if necessary, in hand, the assembly of the final compound requires the formation of two bonds: between C^1 and C^2, and between C^2 and C^3. These bond-forming steps may be taken in either order. Thus, the following sequences can be proposed:

$C^1 + C^2 \rightarrow C^1C^2 \rightarrow C^1C^2C^3$

$C^2 + C^3 \rightarrow C^2C^3 \rightarrow C^1C^2C^3$

(i) Formation of C^1-C^2 bond

The bond between C^1 and C^2 is a simple amide bond. The chemistry for making such bonds from a carboxylic acid and a secondary amine is well known in the art of organic synthesis, and particularly in the field of peptide synthesis. The carboxylic acid may be converted into a more reactive species such as an acid chloride (using, for example oxalyl chloride or thionyl chloride) or a mixed anhydride (using isobutyl chloroformate). This reactive species is then added to the secondary amine in a suitable solvent, generally an aprotic solvent such as dichloromethane or dimethylformamide, in the

presence of a base such as triethylamine or 4-dimethylaminopyridine, and the reaction is allowed to proceed at a temperature between -20°C and the boiling point of the solvent. The choice of temperature and the time allowed for the reaction will depend on the reactivity of the two components.

Alternatively, the carboxylic acid and the secondary amine may be mixed in a suitable solvent as above, optionally in the presence of a base, and a condensing agent added. Suitable condensing agents include carbodiimides, such as dicyclohexylcarbodiimide (DCC) and N-ethyl-N'-dimethylaminopropylcarbodiimide (EDC, also WSCD for water-soluble carbodiimide), phosphorus reagents such as (benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP®) and bromotripyrrolidino-phosphonium hexafluorophosphate (PyBroP®), and ureas such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU).

(ii) Formation of C^2-C^3 bond

The bond between C^2 and C^3 is a carbamate (when X^1 = O) or a urea (when X^1 = NH). The first step in the formation of this bond is generally to react the heterocycle derivative with phosgene or a phosgene equivalent such as trichloromethyl chloroformate, bis(trichloromethyl)carbonate or carbonyldiimidazole. Again, an aprotic solvent and a tertiary amine base will generally be used. The intermediate formed in this step is usually not isolated. The alcohol (X^1 = O) or amine (X^1 = NH) is added and the reaction is allowed to continue, directly forming the carbamate or urea. As an alternative, when X^1 = NH the reactive intermediate may be formed by the reaction of C^2 with the phosgene equivalent and the amine added in the second part of the synthesis.

The compounds according to the present invention are useful in human and animal therapy. When so used, they will generally be formulated in an appropriate manner. Thus a second aspect of the present invention is a pharmaceutical formulation that includes a compound as described above as an active ingredient. A third aspect of the present invention is the use of a compound according to the first aspect in the manufacture of such a composition.

The composition according to the present invention may be presented in any form that is known in the art. For example, the formulation may be presented as a tablet, capsule, powder, suppository, cream, solution or suspension, or in a more complex form such as an adhesive patch. The formulation will generally include one or more excipients, such as diluents, bulking agents, binding agents, dispersants, solvents, preservatives, flavoring agents and the like. Where the formulation is presented as a tablet or capsule the excipients may optionally include one or more agents to control the release of the active species, such as a coating of a polymer that is insoluble at low pH but soluble at neutral or high pH. Such a coating (known as an "enteric coating") prevents the release of the active agent in the stomach but allows its release in the intestines. The formulation may also include one or more additional pharmacologically active species. Preferably the formulation includes no such additional active agents.

In further aspects, the present invention comprises the use of such compositions, and hence of the compounds of the invention, in human and animal therapy, and methods of treatment involving such use of the compositions and compounds. The compounds of the present invention are potent and selective oxytocin receptor agonists, and so the compositions are useful in the treatment of conditions for which inadequate oxytocin-like activity is implicated in the pathophysiology. Such conditions include, but are not limited to: sexual disorders such as male erectile dysfunction, ejaculatory disorders and female sexual dysfunction, cancer of the prostate, breast, ovary and bones, osteoporosis, benign prostatic hyperplasia, post-partum bleeding, and depression. The compositions may also be used to induce labour or delivery of the placenta, to decrease arterial blood pressure, to decrease exaggerated responses to stress and to increase the nociceptive threshold.

In a preferred embodiment, the composition is used to treat male or female sexual dysfunction, and more preferably erectile dysfunction.

When used as therapeutic agents, the compositions of the present invention may be administered by any appropriate route that is known in the art. For example, they may be administered by the oral, buccal, sublingual, rectal, intravaginal, nasal, pulmonary or transdermal routes. Alternatively, they may be given by injection, including intravenous, subcutaneous and intramuscular injection. The amount given will be determined by the attending physician taking into consideration all appropriate factors. Generally a single

dose will comprise between 0.1mg and 1000mg, preferably between 1mg and 250mg, of active compound. The dose may be given on a single occasion or repeatedly. When given repeatedly, it may be given at regular intervals, such as once, twice or three times daily, or on demand, according to the condition being treated.

For long-term treatment an alternative to repeated dosing may be the administration of a depot dose. For this method of administration the active agent is generally introduced into a matrix of biodegradable polymer, such as a copolymer of lactic and glycolic acids, and the formulation is given either *s.c.* or *i.m.* so as to form a deposit from which the active agent is released as the polymer degrades.

The foregoing description is further illustrated in the following examples, which are intended to demonstrate the application of the invention but not to limit the scope thereof.

EXAMPLES

The following abbreviations have been used:

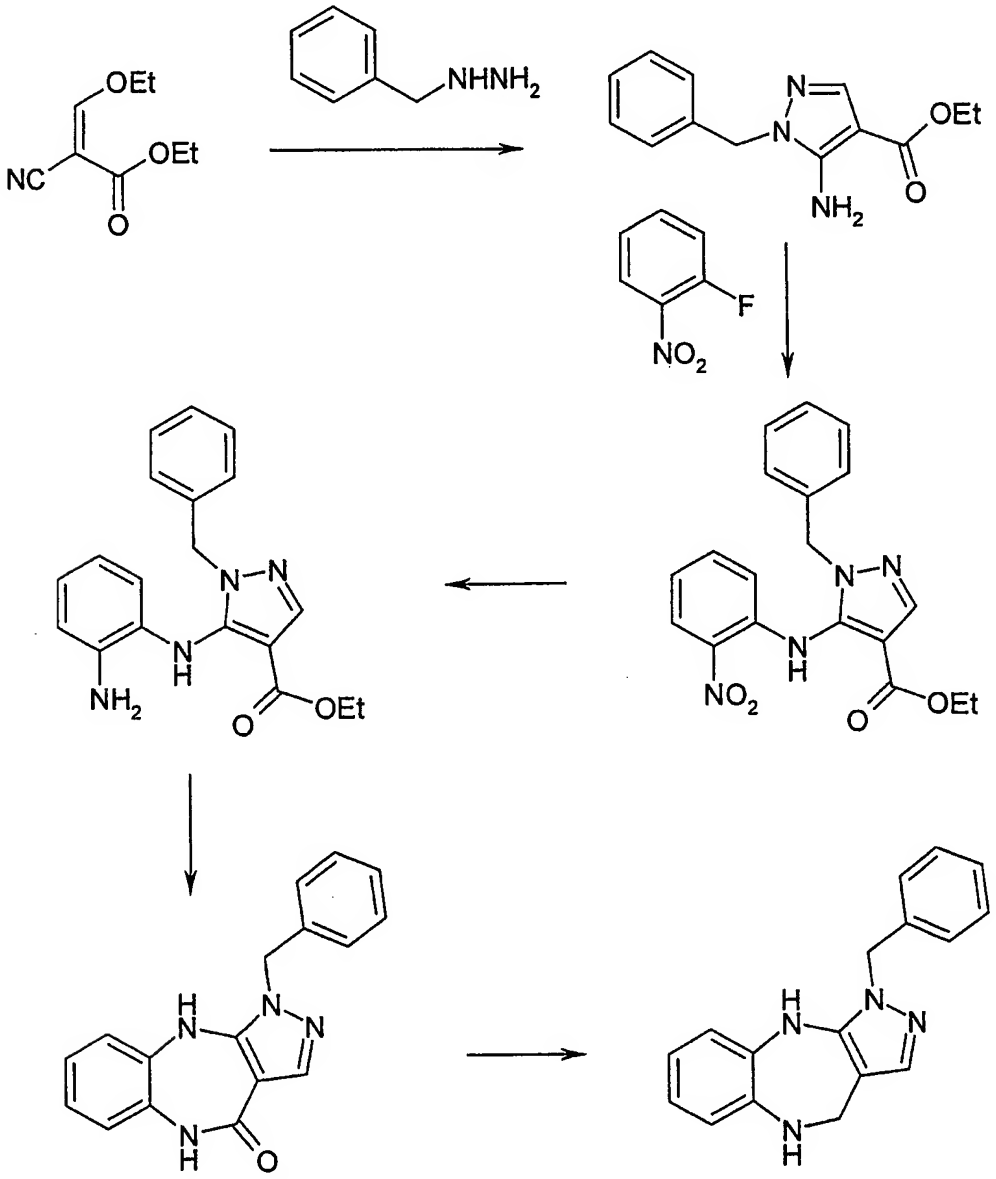
Bu	butyl – alkyl residues may be further denoted as n (normal, i.e. unbranched), i (iso) and t (tertiary)
DIEA	*N,N*-diisopropylethylamine
DMF	dimethylformamide
Et	ethyl
EtOAc	ethyl acetate
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
h	hour(s)
Me	methyl
MS	mass spectrum
NMR	nuclear magnetic resonance spectrum – NMR spectra were recorded in $CDCl_3$ unless otherwise indic;ated
OVA	ornithine vasotocin analogue
pet. ether	petroleum ether boiling in the range 60-80°C
Ph	phenyl
Pn	pentyl
Pr	propyl

THF	tetrahydrofuran
WSCD	water-soluble carbodiimide (*N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride

Examples 1-9 describe the synthesis of intermediates. Compounds according to the present invention are described in Examples 10 to 134.

Example 1

1-Benzyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



1A: Ethyl 5-amino-1-benzylpyrazole-4-carboxylate

Benzylhydrazine dihydrochloride (4.29g, 22mmol) was added to a solution of ethyl (ethoxymethylene)cyanoacetate (3.38g, 20mmol) and triethylamine (6.15ml, 44mmol, 2eq) in ethanol (40ml) and the mixture was heated at reflux for 18h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel

(eluant 60% pet. ether/40% ethyl acetate) to yield a pale yellow solid identified as ethyl 5-amino-1-benzylpyrazole-4-carboxylate (4.3g, 88%).

1B: Ethyl 1-benzyl-5-(2′-nitrophenylamino)pyrazole-4-carboxylate

Sodium hydride (60% dispersion in oil, 520mg, 13mmol) was added portionwise to a suspension of ethyl 5-amino-1-benzylpyrazole-4-carboxylate (2.2g, 9mmol) in anhydrous THF (30ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 2h then 1-fluoro-2-nitrobenzene (1.26g, 9mmol) was added and the resultant deep purple suspension was stirred at room temperature for 18h. 1M $KHSO_4$ was added to quench the reaction and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with 0.3M $KHSO_4$, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 75% pet. ether/25% ethyl acetate) to yield ethyl 1-benzyl-5-(2′-nitrophenylamino)pyrazole-4-carboxylate (2.5g, 76%).

MS $[M+H]^+$ 366.8

1C: Ethyl 5-(2′-aminophenylamino)-1-benzylpyrazole-4-carboxylate

Ethyl 1-benzyl-5-(2′-nitrophenylamino)pyrazole-4-carboxylate (2.5g, 6.8mmol) was dissolved in ethyl acetate/ethanol (1:1, 100ml) and hydrogenated over 10% Pd/C catalyst for 70 minutes. The mixture was filtered through Celite® filter agent and the filtrate was concentrated *in vacuo* to give a white solid identified as ethyl 5-(2′-aminophenylamino)-1-benzylpyrazole-4-carboxylate (1.5g, 86%).

MS $[M+H]^+$ 337.2

1D: 1-Benzyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepin-4(5*H*)-one

A solution of ethyl 5-(2′-aminophenylamino)-1-benzylpyrazole-4-carboxylate (1.75g, 5.2mmol) in acetic acid/ 2-propanol (1:9, 40ml) was heated at reflux for 3 days. The solvent was removed *in vacuo* and the residue was azeotroped with toluene to give an off-white solid that was purified by flash chromatography on silica gel (eluant 35% pet. ether/65% ethyl acetate) to yield a white solid identified as 1-benzyl-4,10-dihydro-pyrazolo[5,4-*b*][1,5]benzodiazepin-4(5*H*)-one (780mg, 52%).

MS $[M+H]^+$ 291.1

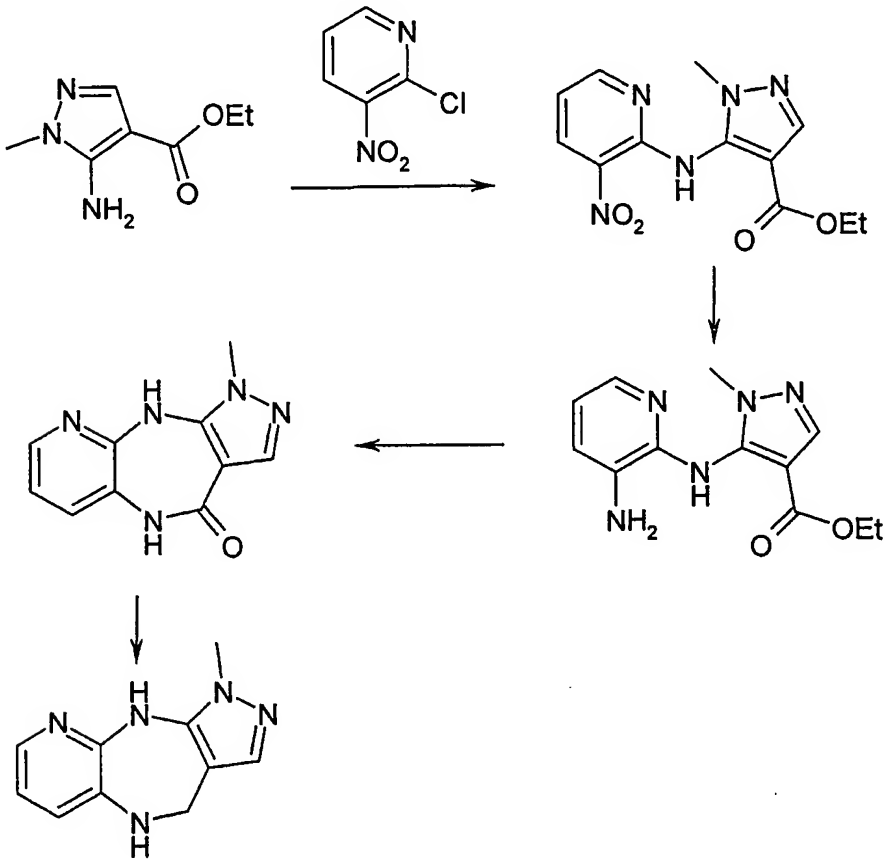
1E: 1-Benzyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

$LiAlH_4$ (365mg, 10mmol) was added portionwise to a suspension of 1-benzyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepin-4(5*H*)-one (780mg, 2.7mmol) in anhydrous THF (15ml) at 0°C over 10min. The resulting suspension was heated at reflux for 18h, then allowed to cool to room temperature. A further portion of $LiAlH_4$ (90mg, 2.5mmol) was added and the mixture was heated at refluxed for 3h. The mixture was cooled to 0°C, 35% ammonia solution (1ml) was added dropwise over 10min and the mixture was stirred at room temperature for 1h. The resulting suspension was filtered through Celite® filter agent and the filtrate was concentrated *in vacuo* to give a white solid identified as 1-benzyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (450mg, 60%).

MS $[M+H]^+$ 276.9

Example 2

1-Methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine



2A: Ethyl 1-methyl-2-(3′-nitro-2′-pyridylamino)pyrazole-4-carboxylate

Sodium hydride (60% dispersion in oil, 600mg, 15mmol) was added portionwise to a suspension of ethyl 5-amino-1-methylpyrazole-4-carboxylate (1.69g, 10mmol) in anhydrous THF (15ml) at 0°C. The mixture was stirred for 2h at room temperature then 2-chloro-3-nitropyridine (1.58g, 10mmol) was added and the resulting deep red suspension was stirred at room temperature for 18h. 1M $KHSO_4$ was added to quench the reaction and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with 0.3M $KHSO_4$, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 30% pet. ether/70% ethyl acetate) to give ethyl 1-methyl-2-(3′-nitro-2′-pyridylamino)pyrazole-4-carboxylate (1.95g, 67%).

MS $[M+H]^+$ 292.0

2B: Ethyl 2-(3′-amino-2′-pyridylamino)-1-methylpyrazole-4-carboxylate

A solution of ethyl 1-methyl-2-(3′-nitro-2′-pyridylamino)pyrazole-4-carboxylate (1.95g, 6.7mmol) in ethanol (100ml) was hydrogenated over 10% Pd/C catalyst for 3h. The reaction mixture was filtered through Celite® filter agent and the filtrate was concentrated *in vacuo* to give a white solid identified as ethyl 2-(3′-amino-2′-pyridylamino)-1-methyl-pyrazole-4-carboxylate (1.5g, 86%).

2C: 1-Methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-one

A solution of ethyl 2-(3′-amino-2′-pyridylamino)-1-methylpyrazole-4-carboxylate (1.5g, 5.75mmol) in acetic acid/2-propanol (1:9, 50ml) was heated at reflux for 3 days. The solvent was removed *in vacuo* and the residue was azeotroped with toluene. The residue was purified by recrystallization from ethanol and then flash chromatography on silica gel (eluant 95% chloroform/4% methanol/1% acetic acid) to give a white solid identified as 1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-one (560mg, 45%).

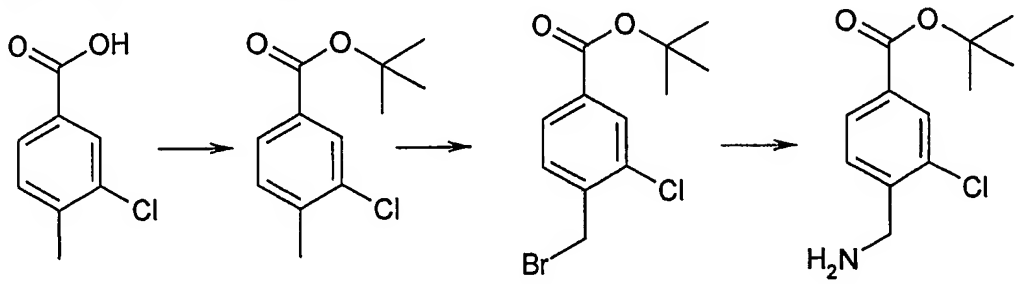
2D: 1-Methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine

LiAlH4 (365mg, 10mmol) was added portionwise to a suspension of 1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-one (560mg, 2.6mmol) in anhydrous THF (30ml) at 0°C over 10 minutes. The resulting suspension was heated at reflux for 18h. The reaction was cooled to 0°C and 35% ammonia solution (1ml) was added dropwise over 10 minutes, then the mixture was stirred at room temperature for 1h. The resulting suspension was filtered through Celite® filter agent and the filtrate was concentrated *in vacuo* to give a white solid identified as 1-methyl-4,10-dihydro-pyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (410mg, 78%).

MS $[M+H]^+$ 202.1.

Example 3

***tert*-Butyl 4-aminomethyl-3-chlorobenzoate**



3A: *tert*-Butyl 3-chloro-4-methylbenzoate

Thionyl chloride (11ml, 150mmol) was added to a suspension of 3-chloro-4-methyl-benzoic acid (5.12g, 30mmol) in toluene (25ml) and the mixture was heated at reflux for 2h. The solvent was removed *in vacuo* and the residue was azeotroped with toluene three times, then dissolved in anhydrous THF (40ml) and cooled to 0°C. Lithium *tert*-butoxide (2.4g, 30mmol) was added and the mixture was stirred at room temperature for 3 days. Water (5ml) was added and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate. The solution was washed with 0.3M $KHSO_4$, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a pale yellow gum identified as *tert*-butyl 3-chloro-4-methylbenzoate (5.4g, 79%).

3B: *tert*-Butyl 4-bromomethyl-3-chlorobenzoate

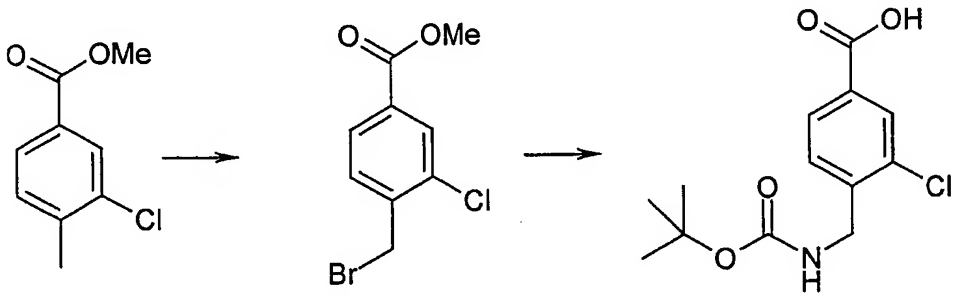
N-Bromosuccinimide (4.27g, 24mmol) and 2,2′-azo-*bis*(2-methylpropionitrile) (394mg, 2.4mmol) were added to a solution of *tert*-butyl 3-chloro-4-methylbenzoate (5.4g, 23.8mmol) in carbon tetrachloride (75ml) and the mixture was heated at reflux for 18h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant 95% pet.ether/5% ethyl acetate) to give a white solid identified as *tert*-butyl 4-bromomethyl-3-chlorobenzoate (5.7g, 78%).

3C: *tert*-Butyl 4-aminomethyl-3-chlorobenzoate

Ethanol (100ml) was saturated with ammonia, then *tert*-butyl 4-bromomethyl-3-chloro-benzoate (5.7g, 18.7mmol) was added and the mixture was stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue was triturated with diethyl ether to give a white solid identified as *tert*-butyl 4-aminomethyl-3-chlorobenzoate (4.1g, 91%).

Example 4

4-(*tert*-Butyloxycarbonylaminomethyl)-3-chlorobenzoic acid



4A. Methyl 4-bromomethyl-3-chlorobenzoate

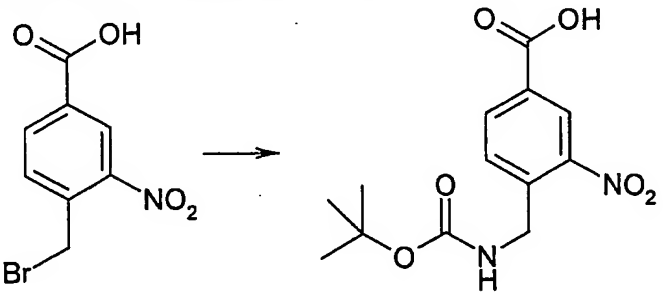
To a solution of methyl 3-chloro-4-methylbenzoate (5.0g, 27.1mmol) in carbon tetrachloride (50ml) were added *N*-bromosuccinimide (5.8g, 32.0mmol) and 2,2'-azo-*bis*(2-methylpropionitrile) (0.442g, 2.70mmol). The mixture was heated at reflux for 18h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (eluant pet. ether → 5% ethyl acetate/95% pet. ether) to give an oil identified as methyl 4-bromomethyl-3-chlorobenzoate (5.96g, 84%).

4B. 4-(*tert*-Butyloxycarbonylaminomethyl)-3-chlorobenzoic acid

To a saturated solution of ammonia in ethanol (170ml) was added methyl 4-bromomethyl-3-chlorobenzoate from Example 4A (5.5g, 20.9mmol). The mixture was stirred at room temperature for 1h and then concentrated *in vacuo*. The residue was triturated with diethyl ether and the resultant white crystals were filtered off and washed with more diethyl ether. To a solution of this solid in water (100ml) were added solutions of di-*tert*-butyl dicarbonate (5.0g, 23.0mmol) in dioxan (100ml) and sodium hydroxide (1.86g, 46.0mmol) in water (100ml). The mixture was stirred at room temperature for 18h and then concentrated *in vacuo*. The aqueous residue was acidified with citric acid and extracted with chloroform/2-propanol. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid identified as 4-(*tert*-butyloxy-carbonylaminomethyl)-3-chlorobenzoic acid (2.8g, 67%).

Example 5

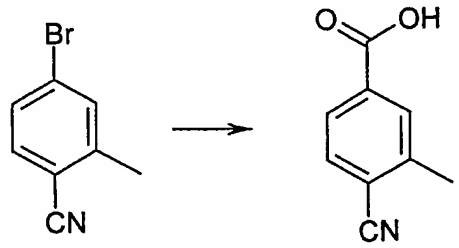
4-(*tert*-Butyloxycarbonylaminomethyl)-3-nitrobenzoic acid



4-Bromomethyl-3-nitrobenzoic acid (4.75g, 18.2mmol) was reacted following the method of Example 4B to give a yellow solid identified as 4-(*tert*-butyloxycarbonylaminomethyl)-3-nitrobenzoic acid (2.6g, 49%).

Example 6

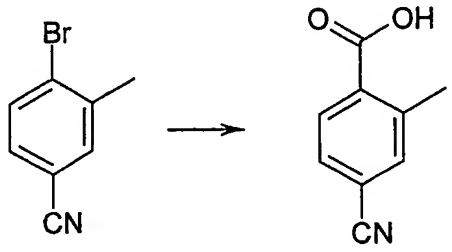
4-Cyano-3-methylbenzoic acid



To a solution of 4-bromo-2-methylbenzonitrile (2.0g, 10.2mmol) in THF (100ml) at –78°C under a nitrogen atmosphere was added dropwise a 2.5M solution of *n*-butyl lithium (4.48ml, 11.2mmol). The mixture was stirred at –78°C for 1h and then poured onto solid carbon dioxide (5g) in THF (50ml). The mixture was allowed to warm to room temperature. Water was added (200ml) and the mixture was extracted with diethyl ether (3 times). The aqueous layer was acidified by addition of concentrated HCl and extracted with chloroform (3 times). The combined chloroform extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid identified as 4-cyano-3-methylbenzoic acid (1.2g, 73%).

Example 7

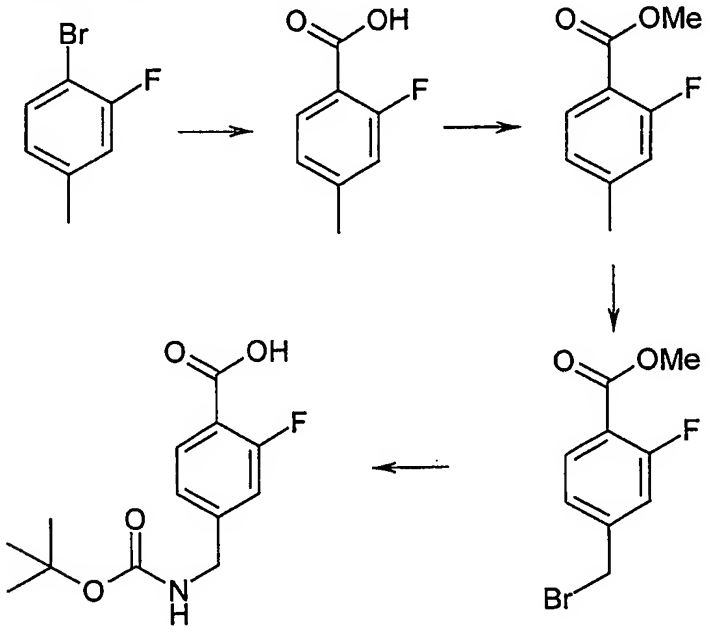
4-Cyano-2-methylbenzoic acid



4-Bromo-3-methylbenzonitrile (2.0g, 10.2mmol) was reacted following the method of Example 6. The product was triturated with hexane to give a yellow solid identified as 4-cyano-2-methylbenzoic acid (0.96g, 59%).

Example 8

4-(*tert*-Butyloxycarbonylaminomethyl)-2-fluorobenzoic acid



8A. 2-Fluoro-4-methylbenzoic acid

4-Bromo-3-fluorotoluene (8.33g, 44.07mmol) was reacted following the method of Example 6 to give a white solid identified as 2-fluoro-4-methylbenzoic acid (4.89g, 72%).

8B. Methyl 2-fluoro-4-methylbenzoate

To a solution of 2-fluoro-4-methylbenzoic acid (6.04g, 39.18mmol) in toluene (80ml) was added thionyl chloride (65ml, 89.11mmol). The mixture was heated at reflux for 2.5h, cooled and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50ml) and methanol (50ml) was added. The mixture was stirred at room temperature for 2.5h and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (100ml), washed with saturated sodium bicarbonate solution and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a tan solid identified as methyl 2-fluoro-4-methylbenzoate (5.07g, 77%).

8C. Methyl 4-bromomethyl-2-fluorobenzoate

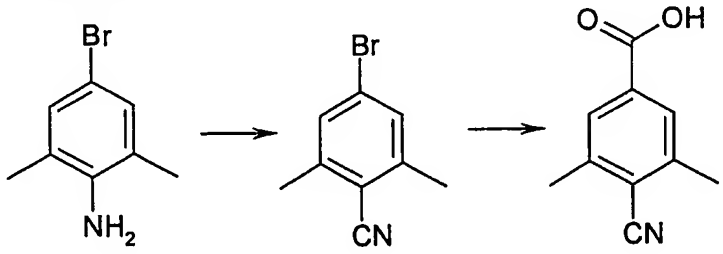
Methyl 2-fluoro-4-methylbenzoate (5.07g, 30.16mmol) was reacted following the method of Example of 4A. The product was purified by flash chromatography on silica (eluant 20% ethyl acetate/ 80% pet. ether) to give an oil identified as methyl 4-bromomethyl-2-fluorobenzoate (5.9g, 80%).

8D. 4-(*tert*-Butyloxycarbonylaminomethyl)-2-fluorobenzoic acid

Methyl 4-bromomethyl-2-fluorobenzoate (5.9g, 24.13mmol) was reacted following the method of Example 4B. The product was recrystallised from dioxan/pet. ether to give white crystals identified as 4-(*tert*-butyloxycarbonylaminomethyl)-2-fluorobenzoic acid (2.46g, 38%).

Example 9

4-Cyano-3,5-dimethylbenzoic acid



9A. 4-Bromo-2,6-dimethylbenzonitrile

4-Bromo-2,6-dimethylaniline (4.49g, 22.4mmol) was taken up in water (25ml) and concentrated hydrochloric acid (8.0ml) was added. The mixture was sonicated to form a fine suspension and then cooled to 0°C. A solution of sodium nitrite (1.67g, 24.2mmol) in

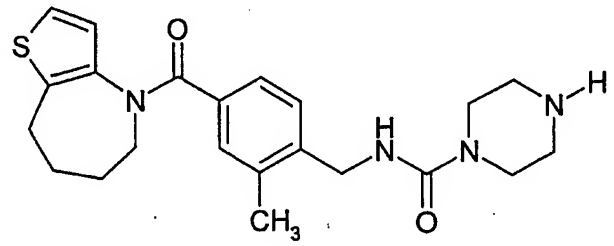
water (5ml) was then added dropwise so as to maintain the temperature of the reaction between 0-5°C. The mixture was stirred at 0-5°C for 30 minutes and then neutralised by addition of solid sodium bicarbonate. The resulting solution was then added portionwise to a solution of copper cyanide (2.42g, 27.0mmol) and potassium cyanide (3.65g, 56.1mmol) in water (25ml) at 70°C. The mixture was stirred at 70°C for 30 minutes, allowed to cool and then extracted with toluene (2 times). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (eluant 5% ethyl acetate/ 95% pet. ether) to give an orange solid identified as 4-bromo-2,6-dimethylbenzonitrile (3.2g, 68%).

9B. 4-Cyano-3,5-dimethylbenzoic acid

4-Bromo-2,6-dimethylbenzonitrile (3.20g, 15.2mmol) was reacted following the method of Example 6 to give a tan solid identified as 4-cyano-3,5-dimethylbenzoic acid (1.5g, 56%).

Example 10

4-(3-Methyl-4-(piperazine-1-carbonylaminomethyl)benzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine hydrochloride



10A: 4-(3-Methyl-4-cyanobenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

Thionyl chloride (5ml, 68.55mmol) was added to a stirred suspension of 4-cyano-3-methylbenzoic acid (1.43g, 8.90mmol) in dichloromethane (20ml). The mixture was heated at reflux for 2h, cooled to room temperature and concentrated *in vacuo*. The residue was azeotroped with dichloromethane then dissolved in dichloromethane 20ml. The resulting solution was slowly added to a stirred solution of 5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1.36g, 8.90mmol) and triethylamine (3.70ml, 26.54mmol) in dichloromethane (30ml). The mixture was stirred at room temperature for 24h, washed with 1M $KHSO_4$, saturated $NaHCO_3$ and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 25% EtOAc/pet. ether)

to give a brown solid identified as 4-(3-methyl-4-cyanobenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1.70g, 71%).

10B: 4-(4-Aminomethyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

Cobalt(II) chloride hexahydrate (2.84g, 11.94mmol) was added to a solution of 4-(3-methyl-4-cyanobenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1.70g, 5.70mmol) in methanol (70ml) at 0°C. Sodium borohydride (2.22g, 58.68mmol) was added portionwise at 0°C and the mixture was stirred at 0°C for 30min then at room temperature for 2h. Saturated ammonium chloride was then added and the mixture was stirred for 30min then concentrated *in vacuo*. The residue was azeotroped with toluene then extracted with chloroform. The extracts were washed with brine and concentrated *in vacuo* to give a white solid identified as 4-(4-aminomethyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1.12g, 65%).

10C: 4-(4-(4-(*tert*-Butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

1,1'-Carbonyldiimidazole (234mg, 1.45mmol) was added to a solution of 4-(4-amino-methyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (400mg, 1.33mmol) and DIEA (0.3ml, 1.72mmol) in DMF (20ml) and the mixture was stirred at room temperature for 30min. *tert*-Butyl piperazine-1-carboxylate (281mg, 1.50mmol) was added and the mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was taken up in chloroform and the solution was washed with 1M $KHSO_4$ and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 75% EtOAc/pet. ether) to give a white solid identified as 4-(4-(4-(*tert*-butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (588mg, 86%).

10D: 4-(3-Methyl-4-(piperazine-1-carbonylaminomethyl)benzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine hydrochloride

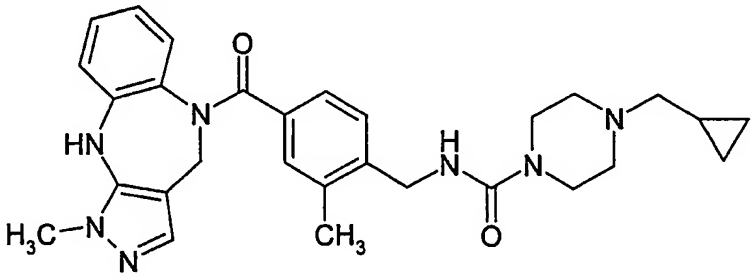
A solution of 4-(4-(4-(*tert*-butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (588mg, 1.15mmol) in 4N HCl/dioxan (10ml) was stirred at room temperature for 30min then concentrated *in vacuo*. The residue was dissolved in acetonitrile/water and lyophilised to give a white solid identified as 4-(3-methyl-4-(piperazine-1-carbonylaminomethyl)benzoyl)-5,6,7,8-tetrahydrothieno-[3,2-*b*]azepine hydrochloride(393mg, 76%).

^{1}H NMR: d_6-DMSO δ 1.60-1.74 (2H, m), 1.82-1.94 (2H, m), 2.17 (3H, s), 2.86-2.95 (2H, m), 2.96-3.10 (4H, m), 3.35-3.45 (2H, m), 3.50-3.64 (4H, m), 4.16 (2H, s), 6.26 (1H, br s), 6.85-7.10 (4H, m), 7.24 (1H, br s), 9.28 (1H, br s) ppm.

MS: $[M+H]^+ = 413.2$

Example 11

5-(4-(4-Cyclopropylmethylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



11A: 5-(4-Cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]-benzodiazepine

Thionyl chloride (1.8ml, 27mmol) was added to a stirred suspension of 4-cyano-3-methyl-benzoic acid (1.29g, 8.0mmol) in toluene (25ml). The mixture was heated at reflux for 2hr, cooled to room temperature and concentrated *in vacuo*. The residue was azeotroped with toluene then dissolved in dichloromethane (10ml). The resulting solution was added to a stirred suspension of 1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (1.6g, 8mmol) and triethylamine (1.4ml, 10mmol) in dichloromethane (15ml). The mixture was stirred overnight at room temperature then concentrated *in vacuo*. The residue was partitioned between chloroform and 0.3M $KHSO_4$. The aqueous phase was extracted with chloroform/2-propanol (80:20). The combined organic phases were washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 5% methanol/chloroform) to give a pale yellow solid identified as 5-(4-cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (2.4g, 87%).

11B: 5-(4-Aminomethyl-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-b][1,5]-benzodiazepine

Cobalt(II) chloride hexahydrate (1.59g, 6.7mmol) was added to an ice-cold solution of 5-(4-cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (1.15g, 3.35mmol) in methanol (35ml). Sodium borohydride (1.27g, 33.5mmol) was added portionwise at 0°C and the mixture was stirred at RT for 1hr, then quenched with 1M $KHSO_4$ and concentrated *in vacuo*. The aqueous residue was diluted with 1M $KHSO_4$ (40ml) and filtered through Celite® filter agent. The filtrate was washed with diethyl ether (2 × 50ml) then basified with 2M NaOH and extracted with chloroform. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give a pale brown solid identified as 5-(4-aminomethyl-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo-[5,4-*b*][1,5]benzodiazepine (745mg, 64%).

11C: 5-(4-(4-(*tert*-Butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

1,1'-Carbonyldiimidazole (76mg, 0.47mmol) was added to a solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzo-diazepine (150mg, 0.43mmol) and DIEA (0.1ml, 0.57mmol) in DMF (10ml). The solution was stirred for 30min, *tert*-butyl piperazine-1-carboxylate (91mg, 0.49mmol) was added and stirring was continued for 72h. The mixture was concentrated *in vacuo* and the residue was taken up in chloroform. The solution was washed with water and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 100% EtOAc then 10%methanol/EtOAc) to give a white solid identified as 5-(4-(4-(*tert*-butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (160mg, 66%).

11D: 1-Methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride

A solution of 5-(4-(4-(*tert*-butyloxycarbonyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (160mg, 0.29mmol) in 4N HCl/dioxan (15ml) was stirred at room temperature for 30min then concentrated *in vacuo*. The residue was azeotroped with diethyl ether to give a white solid identified as 1-methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydro-pyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride (130mg, 90%).

11E: 5-(4-(4-Cyclopropylmethylpiperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

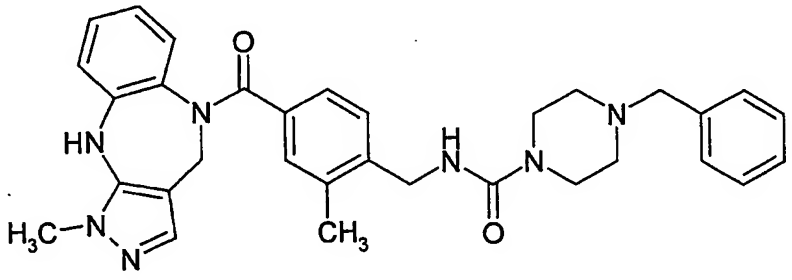
To a solution of 1-methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride (100mg, 0.20mmol) and triethylamine (0.5ml, 3.59mmol) in THF (10ml) were added cyclopropanecarboxaldehyde (14mg, 0.20mmol) and sodium cyanoborohydride (15mg, 0.24mmol) and the resulting mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the resulting solution was washed with saturated $NaHCO_3$, water and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 10% methanol/EtOAc) to give a white solid identified as 5-(4-(4-cyclopropylmethylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (35mg, 35%).

^{1}H NMR: d_4-MeOH δ 0.14 (2H, q, J=4.7Hz), 0.51-0.59 (2H, m), 0.82-0.95 (1H, m), 2.15 (3H, s), 2.28 (2H, d, J=6.7Hz), 2.52 (4H, t, J=4.9Hz), 3.43 (4H, t, J=4.9Hz), 3.80 (3H, s), 3.95 (1H, d, J=14.4Hz), 4.23 (2H, s), 5.78 (1H, d, J=14.6Hz), 6.61-6.74 (2H, m), 6.99 (2H, s), 7.03 (1H, s), 7.05-7.14 (1H, m), 7.19-7.24 (2H, m) ppm.

MS: $[M+H]^+ = 514.3$

Example 12

5-(4-(4-Benzylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



To a solution of 1-methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride (100mg, 0.20mmol) and triethylamine (0.5ml, 3.59mmol) in THF (10ml) were added benzaldehyde (21mg,

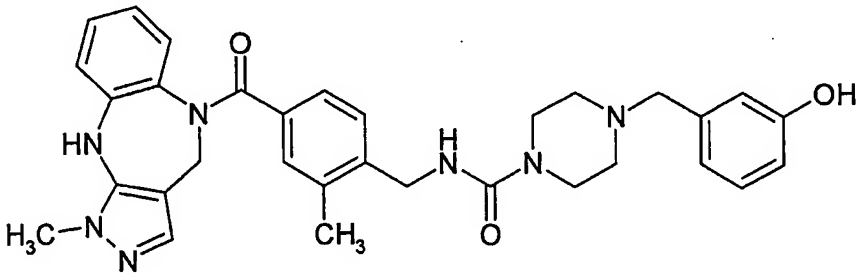
0.20mmol) and sodium cyanoborohydride (15mg, 0.24mmol) and the resulting mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the resulting solution was washed with saturated $NaHCO_3$, water and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 5% methanol/EtOAc) to give a white solid identified as 5-(4-(4-benzylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (37mg, 34%).

^{1}H NMR: δ 2.10 (3H, s), 2.36-2.48 (4H, m), 3.29-3.44 (4H, m), 3.48-3.51 (2H, m), 3.76 (3H, s), 3.96 (1H, d, J=14.6Hz), 4.22-4.28 (2H, m), 4.61-4.68 (1H, m), 5.88 (1H, d, J=14.6Hz), 6.46 (1H, s,) 6.62-6.74 (2H, m), 6.82-6.96 (3H, m), 6.98-7.11 (2H, m), 7.19-7.34 (5H, m) ppm.

MS: $[M+H]^+$ = 550.2

Example 13

5-(4-(4-(3-Hydroxybenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



13A: 3-(*tert*-Butyldimethylsilyloxy)toluene

tert-Butyldimethylsilyl chloride (3.00g, 22.00mmol) was added to a solution of *m*-cresol (2.00g, 18.00mmol) and triethylamine (4ml, 28.7mmol) in dichloromethane (50ml) at 0°C. The mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 10% EtOAc/pet. ether) to give a colourless oil identified as 3-(*tert*-butyldimethylsilyloxy)toluene (3.60g, 88%).

13B: 3-(*tert*-Butyldimethylsilyloxy)benzyl bromide

N-Bromosuccinimide (2.90g, 16.20mmol) and AIBN (266mg, 1.62mmol) were added to a stirred solution of 3-(*tert*-butyldimethylsilyloxy)toluene (3.60g, 16.20mmol) in carbon tetrachloride (120ml) and the mixture was heated at reflux for 24h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant cyclohexane) to give a colourless oil identified as 3-(*tert*-butyldimethylsilyloxy)benzyl bromide (2.45g, 50%).

13C: *tert*-Butyl 4-(3-hydroxybenzyl)piperazine-1-carboxylate

Sodium hydride (406mg, 60% dispersion in oil, 10.15mmol) was added portionwise to a stirred solution of *tert*-butyl piperazine-1-carboxylate in DMF (50ml) at 0°C. The mixture was allowed to warm to room temperature over 1h, then a solution of 3-(*tert*-butyldimethylsilyloxy)benzyl bromide (2.44g, 8.10mmol) in DMF (10ml) was added dropwise and the mixture was stirred at room temperature for 24h. Water was added and the mixture was stirred for 30min then poured into EtOAc. The organic phase was washed with saturated $NaHCO_3$ and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 40% EtOAc/pet. ether) to give a light brown oil identified as *tert*-butyl 4-(3-hydroxybenzyl)piperazine-1-carboxylate (2.00g, 84%).

13D: 1-(3-Hydroxybenzyl)piperazine dihydrochloride

A solution of *tert*-butyl 4-(3-hydroxybenzyl)piperazine-1-carboxylate (1.94g, 6.60mmol) in 4N HCl/dioxan (10ml) was stirred at room temperature for 30min then concentrated *in vacuo*. The residue was triturated with diethyl ether to give a white solid identified as 1-(3-hydroxybenzyl)piperazine dihydrochloride (1.10g, 63%).

13E: 5-(4-(4-(3-Hydroxybenzyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

1,1'-Carbonyldiimidazole (15mg, 0.09mmol) was added to a stirred solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzo-diazepine (31mg, 0.09mmol) and DIEA (0.1ml 0.57mmol) in DMF (5ml). The solution was stirred for 1h, 1-(3-hydroxybenzyl)piperazine dihydrochloride (27mg, 0.10mmol) was added and stirring was continued at room temperature for 24h. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, then concentrated *in vacuo*. The residue was

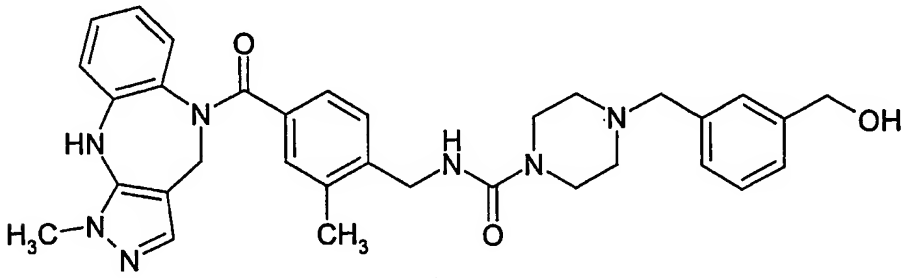
purified by flash chromatography on silica gel (eluant 20% methanol/EtOAc) to give a white solid identified as 5-(4-(4-(3-hydroxybenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (45mg, 90%).

^{1}H NMR: δ 2.15 (3H, s), 2.41 (4H, t, J=4.7Hz), 3.40 (4H, t, J=4.7Hz), 3.46 (2H, s), 3.80 (3H, s), 3.97 (1H, d, J=14.6Hz), 4.22 (2H, s), 4.90 (1H, m), 5.78 (1H, d, J=14.6Hz), 6.62-6.79 (5H, m), 6.99 (2H, s), 7.03-7.27 (6H, m) ppm.

MS: $[M+H]^+$ = 566.1

Example 14

5-(4-(4-(3-Hydroxymethylbenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



14A: *tert*-Butyl 4-(3-(methyloxycarbonyl)benzyl)piperazine-1-carboxylate

Methyl 3-(bromomethylbenzoate) (1.23g, 5.37mmol) was added to a stirred solution of *tert*-butyl piperazine-1-carboxylate (1.00g, 5.37mmol) and triethylamine (1.50ml, 10.74mmol) in dichloromethane (20ml). The solution was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc) to give a white solid identified as *tert*-butyl 4-(3-(methyloxycarbonyl)benzyl)piperazine-1-carboxylate (1.55g, 86%).

14B: *tert*-Butyl 4-(3-carboxybenzyl)piperazine-1-carboxylate

Lithium hydroxide monohydrate (339mg, 9.27mmol) was added to a solution of *tert*-butyl 4-(3-(methyloxycarbonyl)benzyl)piperazine-1-carboxylate (1.55g, 4.63mmol) in THF (10ml) and water (2ml). The solution was stirred at room temperature for 24h then acidified to pH 5 with 0.3M $KHSO_4$ and extracted successively with chloroform and

dichloromethane. The combined extracts were concentrated *in vacuo* to give a white solid identified as *tert*-butyl 4-(3-carboxybenzyl)piperazine-1-carboxylate (1.09g, 74%).

14C: *tert*-Butyl 4-(3-(hydroxymethyl)benzyl)piperazine-1-carboxylate

Isobutyl chloroformate (0.47ml, 3.64mmol) was slowly added to an ice-cold solution of *tert*-butyl 4-(3-carboxybenzyl)piperazine-1-carboxylate (1.06g, 3.31mmol) and *N*-methylmorpholine (0.80ml, 7.28mmol) in THF (15ml). The solution was stirred at 0°C for 45min and then filtered. The filtrate was added to an ice-cold solution of sodium borohydride (313mg, 8.27mmol) in water (10ml). The stirred mixture was allowed to warm to room temperature over 2h and then concentrated *in vacuo*. The residue was taken up in EtOAc and the solution was washed with water and brine then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant-EtOAc) to give a white solid identified as *tert*-butyl 4-(3-(hydroxymethyl)benzyl)piperazine-1-carboxylate (230mg, 23%).

14D: 1-(3-(Hydroxymethyl)benzyl)piperazine dihydrochloride

A solution of *tert*-butyl 4-(3-(hydroxymethyl)benzyl)piperazine-1-carboxylate (230mg, 0.75mmol) in 4N HCl/dioxan (10ml) was stirred at room temperature for 45min then concentrated *in vacuo*. The residue was azeotroped with toluene to give a white solid identified as 1-(3-(hydroxymethyl)benzyl)piperazine dihydrochloride (158mg, 75%).

14E: 5-(4-(4-(3-Hydroxymethylbenzyl)piperazine-1-carbonylaminomethyl)-3-methyl-benzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

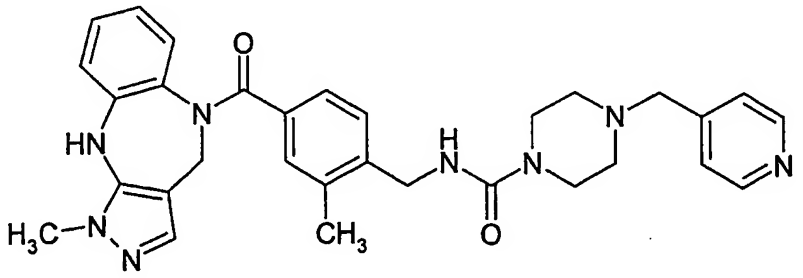
1,1'-Carbonyldiimidazole (20mg, 0.12mmol) was added to a solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzo-diazepine (35mg, 0.10mmol) in DMF (3ml). The solution was stirred for 1h, a solution of 1-(3-(hydroxymethyl)benzyl)piperazine dihydrochloride (31mg, 0.11mmol) and DIEA (54µl, 0.30mmol) in DMF (2ml) was added and the mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue taken up in chloroform and the solution was washed with brine and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 7% methanol/chloroform) to give a white solid identified as 5-(4-(4-(3-hydroxymethylbenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (27mg, 50%).

^{1}H NMR: δ 2.00 (3H, s), 2.32-2.36 (4H, m), 3.32-3.45 (4H, m), 3.46 (2H, s), 3.63 (3H, s), 3.91 (1H, d, J=14.6Hz), 4.10-4.20 (1H, m), 4.66 (2H, s), 5.28-5.29 (1H, m), 5.80 (1H, d, J=14.3Hz), 6.50-7.30 (15H, m) ppm.

MS: $[M+H]^+$ = 580.3

Example 15

1-Methyl-5-(3-methyl-4-(4-(4-picolyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



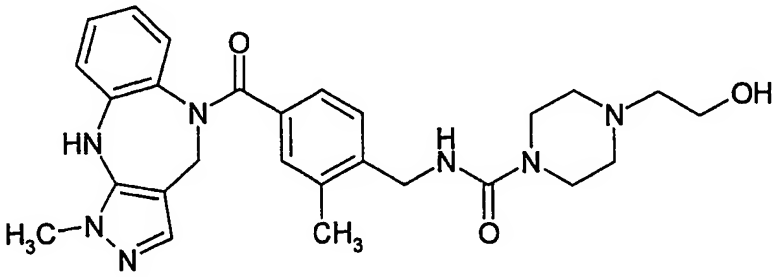
To a solution of 1-methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride (100mg, 0.20mmol) and triethylamine (0.5ml, 3.59mmol) in THF (10ml) were added 4-pyridinecarboxaldehyde (21mg, 0.20mmol) and sodium cyanoborohydride (15mg, 0.24mmol) and the resulting mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the resulting solution was washed with saturated $NaHCO_3$, water and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 10%-30% methanol/EtOAc) to give a white solid identified as 1-methyl-5-(3-methyl-4-(4-(4-picolyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (33mg, 30%).

^{1}H NMR: δ 2.13 (3H, s), 2.34-2.49 (4H, m), 3.29-3.47 (4H, m), 3.76 (3H, s), 3.96 (1H, d, J=14.8Hz), 4.25-4.27 (2H, d, J=4.7Hz), 4.50-4.60 (1H, m), 5.90 (1H, d, J=14.4Hz), 6.25 (1H, s), 6.63-6.71 (2H, m), 6.84 (2H, s), 6.92 (1H, s), 7.00-7.12 (2H, m), 7.25 (5H, s), 8.53 (2H, d, J=5.9Hz) ppm.

MS: $[M+H]^+ = 551.1$

Example 16

5-(4-(4-(2-Hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



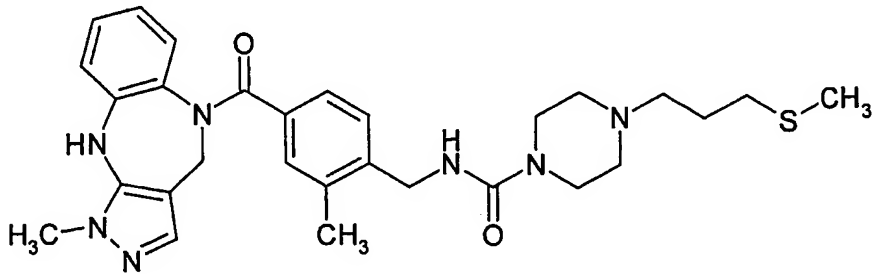
1,1'-Carbonyldiimidazole (20mg, 0.19mmol) was added to a solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (31mg, 0.09mmol) in DMF (3ml). The solution was stirred at room temperature for 1h, a solution of 1-(2-hydroxyethyl)piperazine (13mg, 0.10mmol) in DMF (2ml) was added and stirring was continued for 72h. The solution was concentrated *in vacuo* and the residue was partitioned between chloroform and brine. The organic layer was separated and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 7% methanol/chloroform) to give a white solid identified as 5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (22mg, 48%).

^{1}H NMR: δ 2.09 (3H, s), 2.42-2.59 (6H, m), 2.91-3.01 (1H, m), 3.33-3.62 (6H, m), 3.67 (3H, s), 3.93-3.98 (1H, m), 4.20-4.23 (2H, m), 5.00-5.03 (1H, m), 5.84-5.90 (1H, m), 6.64-7.25 (9H, m) ppm.

MS: $[M+H]^+ = 504.2$

Example 17

1-Methyl-5-(3-methyl-4-(4-(3-(methylthio)propyl)piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



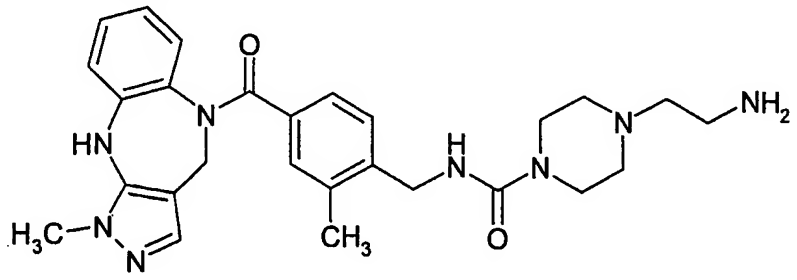
To a solution of 1-methyl-5-(3-methyl-4-(piperazine-1-carbonylaminomethyl)-benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine hydrochloride (100mg, 0.20mmol) and triethylamine (0.5ml, 3.59mmol) in THF (10ml) were added 3-(methylthio)-propionaldehyde (21mg, 0.20mmol) and sodium cyanoborohydride (15mg, 0.24mmol) and the resulting mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the resulting solution was washed with saturated $NaHCO_3$, water and brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 20% methanol/EtOAc) to give a white solid identified as 1-methyl-5-(3-methyl-4-(4-(3-(methylthio)-propyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]-benzodiazepine (41mg, 38%).

^{1}H NMR: δ 1.63-1.80 (3H, m), 2.04-2.12 (4H, m), 2.33-2.42 (6H, m), 2.48 (2H, t, J=6.7Hz), 3.29-3.39 (4H, m), 3.71 (3H, s), 3.93 (1H, d, J=14.4Hz), 4.12-4.30 (2H, m), 4.57-4.70 (1H, m), 5.85 (1H, d, J=14.6Hz), 6.44 (1H, s), 6.59-6.71 (2H, m), 6.83-6.88 (2H, m), 6.92-7.08 (2H, m), 7.14-7.27 (2H, m) ppm.

MS: $[M+H]^+ = 548.0$

Example 18

5-(4-(4-(2-Aminoethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine dihydrochloride



18A: Benzyl 4-(2-hydroxyethyl)piperazine-1-carboxylate

Benzyl chloroformate (3.40ml, 24.00mmol) was slowly added to an ice-cold stirred solution of 1-(2-hydroxyethyl)piperazine (2.60g, 20.00mmol) and DIEA (7.0ml, 40.0mmol) in dichloromethane (75ml). The mixture was allowed to warm to room temperature and stirred for 24h then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 6% methanol/chloroform) to give a colourless gum identified as benzyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (4.80g, 91%).

18B: Benzyl 4-(2-bromoethyl)piperazine-1-carboxylate

Carbon tetrabromide (7.23g, 21.80mmol) was added to an ice-cold stirred solution of benzyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (4.80g, 18.20mmol) in dichloromethane (50ml). The solution was stirred for 5min, triphenylphosphine (5.95g, 22.70mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 3h. Silica gel was added and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 50% EtOAc/pet. ether) to give a colourless gum identified as benzyl 4-(2-bromoethyl)piperazine-1-carboxylate (3.45g, 58%).

18C: Benzyl 4-(2-(*tert*-butyloxycarbonylamino)ethyl)piperazine-1-carboxylate

Benzyl 4-(2-bromoethyl)piperazine-1-carboxylate (3.45g, 10.55mmol) was added to an ice-cold saturated solution of ammonia in ethanol (60ml). The mixture was allowed to warm to room temperature and stirred for 4h, then concentrated *in vacuo*. The residue was triturated with diethyl ether. The resultant solid was suspended in dichloromethane (75ml) and triethylamine (2.25ml, 16.00mmol). The suspension was cooled to 0°C and

di-*tert*-butyl dicarbonate (2.40g, 11.00mmol) was added. The mixture was allowed to warm to room temperature and stirred for 24h then concentrated *in vacuo*. The residue was taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 3% methanol/chloroform) to give a yellow gum identified as benzyl 4-(2-(*tert*-butyloxycarbonylamino)ethyl)piperazine-1-carboxylate (2.60g, 68%).

18D: *tert*-Butyl 2-(1-piperazinyl)ethylcarbamate

Hydrogen was passed through a degassed solution of benzyl 4-(2-(*tert*-butyloxycarbonylamino)ethyl)piperazine-1-carboxylate (2.60g, 7.16mmol) in methanol (50ml) containing 10% palladium on carbon (500mg) for 2h. The reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo* to give a yellow gum identified as *tert*-butyl 2-(1-piperazinyl)ethylcarbamate (1.60g, 97%).

18E: 5-(4-(4-(2-(*tert*-Butyloxycarbonylaminoethyl)piperazine-1-carbonylamino-methyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine

1,1'-Carbonyldiimidazole (25mg, 0.15mmol) was added to a solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzo-diazepine (31mg, 0.09mmol) and DIEA (0.1ml, 0.57mmol) in DMF (5ml). The solution was stirred for 1h, *tert*-butyl 2-(1-piperazinyl)ethylcarbamate (22mg, 0.10mmol) was added and stirring was continued at room temperature for 24h. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 20% methanol/EtOAc) to give a white solid identified as 5-(4-(4-(2-(*tert*-butyloxycarbonylaminoethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]-benzodiazepine (44mg, 81%).

18F: 5-(4-(4-(2-Aminoethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine dihydrochloride

A solution of 5-(4-(4-(2-(*tert*-butyloxycarbonylaminoethyl)piperazine-1-carbonylamino-methyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (42mg, 0.07mmol) in 4N HCl/dioxan (5ml) was stirred at room temperature for 30min then concentrated *in vacuo*. The residue was dissolved in acetonitrile/water and lyophilised to give a white solid identified as 5-(4-(4-(2-aminoethyl)piperazine-1-carbonylaminomethyl)-

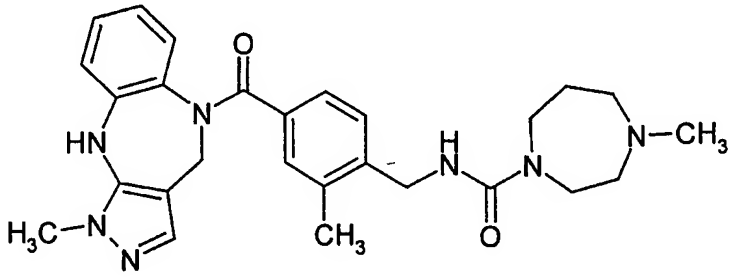
3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine dihydrochloride (37mg, 92%).

^{1}H NMR: δ 2.17 (3H, s), 3.30-3.35 (4H, m), 3.41-3.50 (1H, m), 3.56-3.72 (4H, m), 4.00 (3H, s), 4.04 (1H, s), 4.26 (2H, s), 4.83-4.89 (2H, m), 5.88 (1H, d, J=15Hz), 6.83-6.84 (2H, m), 6.92-7.13 (4H, m), 7.15-7.28 (1H, m), 7.36 (1H, d, J=7.9Hz), 7.96 (1H, s) ppm.

MS: $[M+H]^+$ = 503.5

Example 19

1-Methyl-5-(3-methyl-4-(4-methylperhydro-1,4-diazepine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine



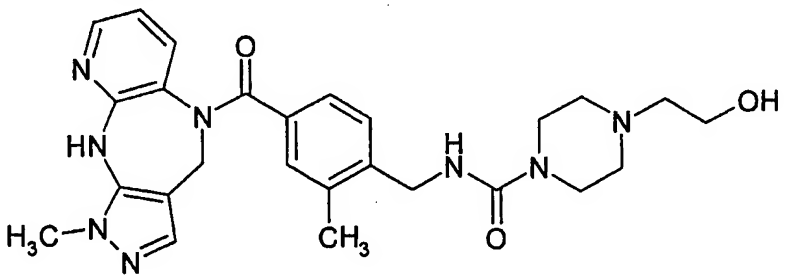
1,1'-Carbonyldiimidazole (37mg, 0.23mmol) was added to a solution of 5-(4-(aminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (75mg, 0.22mmol) in DMF (2ml). The solution was stirred for 1h, a solution of 1-methylhomopiperazine (27mg, 0.24mmol) and DIEA (31mg, 0.24mmol) in DMF (1ml) was added and stirring was continued for 24h. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (eluant 30/2/1 – 1/1/1 chloroform/methanol/concentrated ammonia) to give a white solid identified as 1-methyl-5-(3-methyl-4-(4-methylperhydro-1,4-diazepine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine (38mg, 36%).

^{1}H NMR: δ 1.80-1.99 (2H, m), 2.10 (3H, s), 2.35 (3H, s), 2.51-2.69 (4H, m), 3.39 (2H, t, J=5.9Hz), 3.45-3.68 (2H, m), 3.63 (3H, s), 3.95 (1H, d, J=14.6Hz), 4.23 (2H, t, J=4.2Hz), 4.65-4.75 (1H, m), 5.85 (1H, d, J=14.6Hz), 6.65-6.75 (2H, m), 6.76-6.88 (2H, m), 6.90-7.09 (2H, m), 7.11-7.22 (2H, m) ppm.

MS: [M+H]+ = 488.2

Example 20

5-(4-(4-(2-Hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine



20A: 5-(4-Cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine

Thionyl chloride (0.6ml, 9.00mmol) was added to a suspension of 4-cyano-3-methylbenzoic acid (322mg, 2.00mmol) in toluene (10ml). The mixture was heated at reflux for 2h, allowed to cool and concentrated *in vacuo*. The residue was azeotroped with toluene and then taken up in dichloromethane (5ml). The solution was added slowly to a stirred solution of 1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (400mg, 2.00mmol) and triethylamine (0.35ml, 2.50mmol) in dichloromethane (5ml). The mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 5% methanol/chloroform) to give an orange solid identified as 5-(4-cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (500mg, 73%).

20B: 5-(4-Aminomethyl-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine

Cobalt(II) chloride hexahydrate (690mg, 2.90mmol) was added to an ice-cold stirred solution of 5-(4-cyano-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (500mg, 1.45mmol) in methanol (15ml). Sodium borohydride (570mg, 15.00mmol) was added portionwise and the mixture was stirred at room temperature for 1h. 1M $KHSO_4$ was added, the methanol was removed *in vacuo*, and the aqueous

residue was filtered through Celite®. The filtrate was washed with diethyl ether, basified to pH12 with 2M sodium hydroxide and extracted with chloroform. The chloroform extracts were washed with brine and concentrated *in vacuo* to give a pale orange solid identified as 5-(4-aminomethyl-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (400mg, 79%).

20C: 5-(4-(4-(2-Hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine

1,1'-Carbonyldiimidazole (20mg, 0.12mmol) was added to a solution of 5-(4-aminomethyl-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]-diazepine (35mg, 0.10mmol) in DMF (3ml). The solution was stirred for 1h, a solution of 1-(2-hydroxyethyl)piperazine (13mg, 0.10mmol) and DIEA (18µl, 0.10mmol) in DMF (2ml) was added and the mixture was stirred at room temperature for 24h then concentrated *in vacuo*. The residue taken up in chloroform and the solution was washed with brine and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant 7% methanol/chloroform) to give a pale yellow solid identified as 5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine (29mg, 58%).

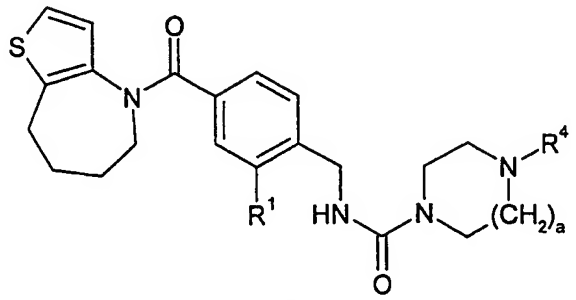
^{1}H NMR: δ 2.42 (3H, br s), 2.44-2.60 (7H, m), 3.20-3.40 (4H, m), 3.55-3.65 (2H, m), 3.79 (3H, s), 3.85-4.00 (1H, m), 4.26 (2H, br s), 4.88 (1H, br s), 5.80-5.95 (1H, m), 6.60 (1H, br s), 6.80- 7.30 (6H, m), 8.00 (1H, s) ppm.

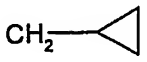
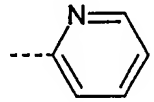
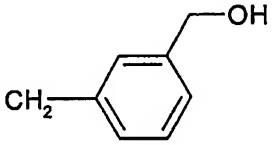
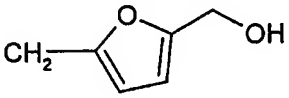
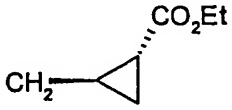
MS: $[M+H]^+$ = 505.2

Examples 21 – 134

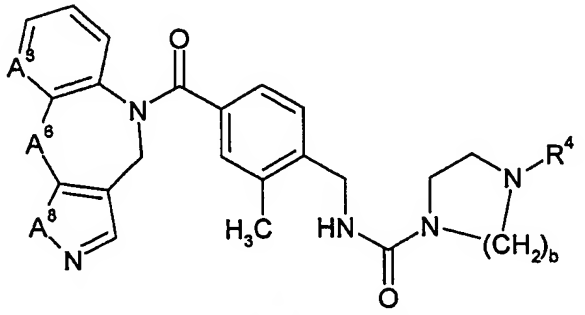
The following compounds were prepared using analogous methods to those described

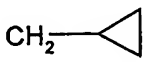
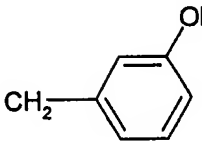
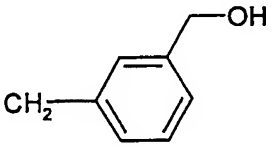
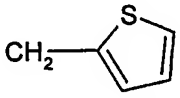
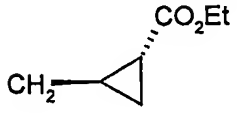
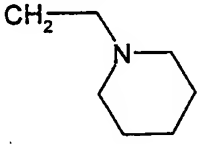
Examples 21 - 30



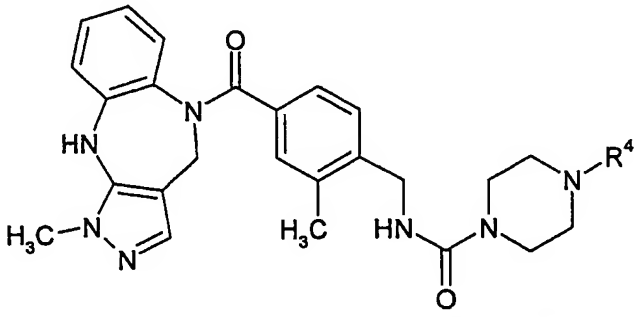
	a	R^1	R^4	MS: $[M+H]^+$
21	1	Cl	CH_3	447.3
22	2	Cl	CH_3	461.3
23	1	Me	$CH_2CH_2CH_2CH_3$	469.3
24	1	Me	$CH_2CH(CH_3)CH_2CH_3$	483.3
25	1	Me		467.3
26	1	Cl		510.3
27	1	Me		533.3
28	1	Me		523.2
29	1	Me		539.3
30	1	Me	CH_2CH_2OH	457.2

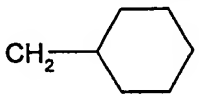
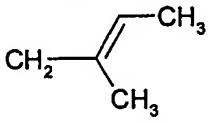
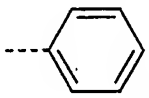
Examples 31 - 46

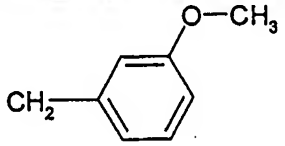
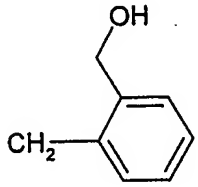
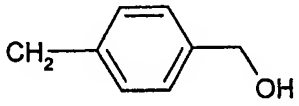
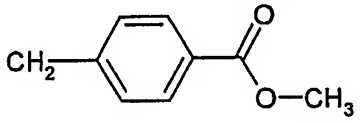
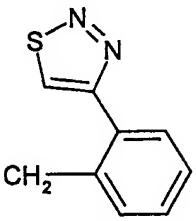
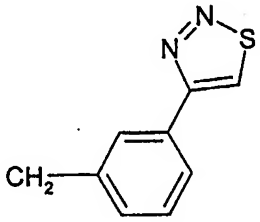
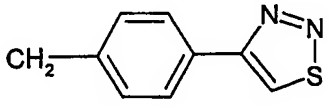
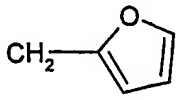
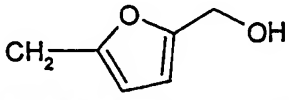


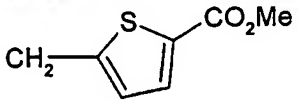
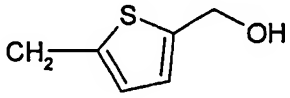
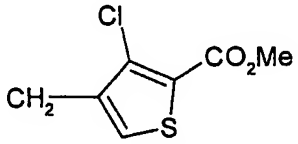
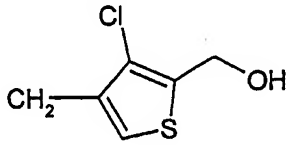
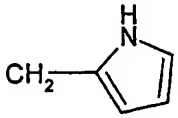
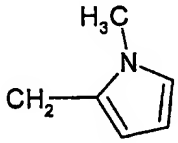
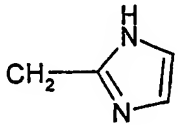
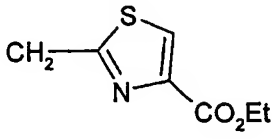
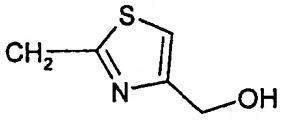
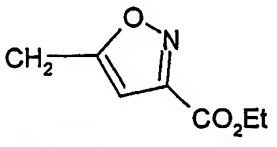
	A^3	A^6	A^8	b	R^4	MS: $[M+H]^+$
31	CH	NH	N-Me	3	H	474.1
32	CH	NH	N-Me	3	$CH_2CH(CH_3)CH_2CH_3$	544.3
33	CH	NH	N-Me	3	$CH_2C(CH_3)_3$	544.3
34	CH	NH	N-Me	3		528.3
35	CH	N-Me	N-Me	1		514.3
36	N	NH	N-Me	2		680.2
37	CH	N-Me	N-Me	2		594.3
38	CH	NH	N-Me	3		570.3
39	CH	NH	N-Me	2		556.3
40	CH	NH	N-Me	3		600.3
41	CH	NH	N-Me	2		586.3
42	N	NH	N-Me	2	$CH_2CH_2NH_2$	504.1
43	N	NH	N-Me	2	$CH_2CH_2CH_2NH_2$	518.3
44	CH	NH	N-Me	2		571.4
45	N	NH	N-Me	2		572.3
46	CH	NH	N-CH_2Ph	2	CH_2CH_2OH	580.2

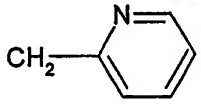
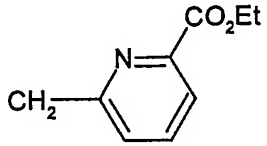
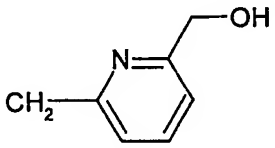
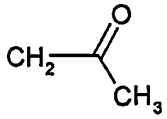
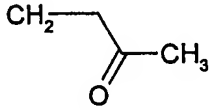
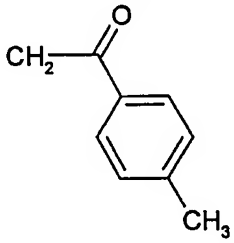
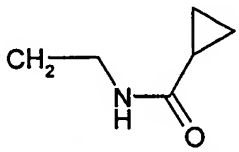
Examples 47 - 117

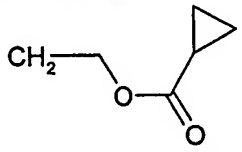
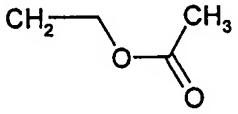
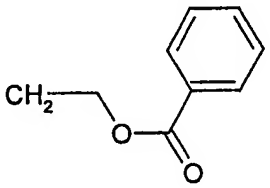
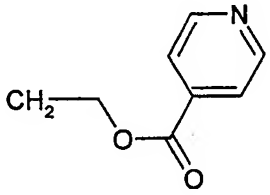
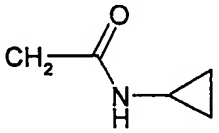
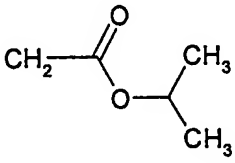
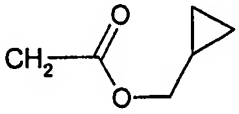
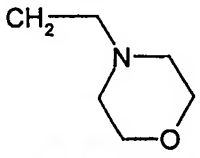


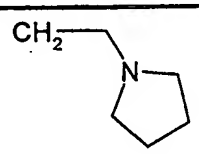
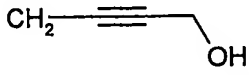
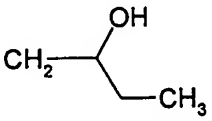
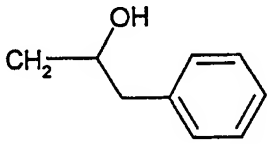
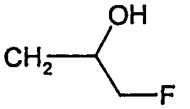
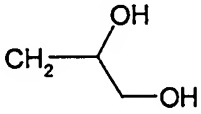
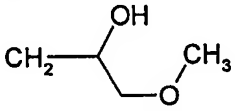
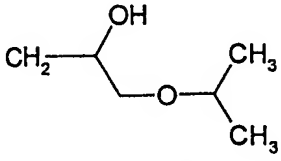
	R^4	MS: $[M+H]^+$
47	H	460.2
48	CH_3	474.2
49	CH_2CH_3	488.2
50	$CH_2CH_2CH_3$	502.3
51	$CH_2CH_2CH_2CH_3$	516.3
52	$CH_2CH_2CH_2CH_2CH_3$	530.3
53	$CH_2CH_2CH_2CH_2CH_2CH_3$	544.3
54	$CH_2CH_2CH(CH_3)_2$	530.3
55	$CH_2CH(CH_3)CH_2CH_3$	530.3
56	$CH_2CH(CH_2CH_3)_2$	544.3
57	$CH_2CH_2C(CH_3)_3$	544.2
58		556.3
59	$CH_2CH=CH_2$	500.1
60		528.3
61		536.2

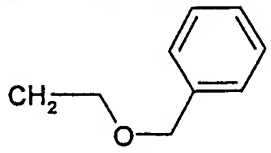
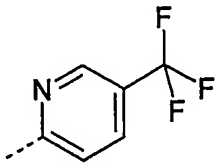
	R^4	MS: $[M+H]^+$
62		580.3
63		580.3
64		580.2
65		608.3
66		634.2
67		634.2
68		634.2
69		540.3
70		570.2

	R^4	MS: $[M+H]^+$
71		614.2
72		586.3
73		648.2
74		620.2
75		538.2
76		553.1
77		540.2
78		629.2
79		587.3
80		599.2

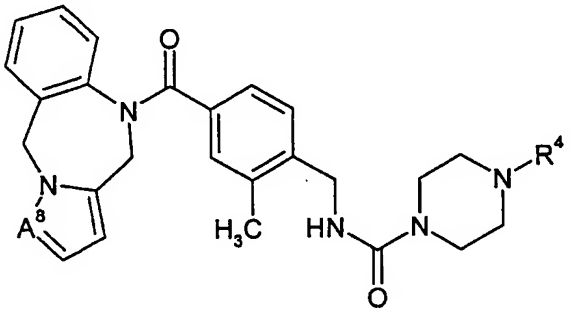
	R^4	MS: $[M+H]^+$
81		551.3
82		609.1
83		581.3
84		516.3
85		530.2
86		592.2
87	$CH_2CH_2CO_2CH_3$	546.3
88	$CH_2CH_2CO_2H$	532.1
89	$CH_2CH_2CH_2CO_2CH_3$	560.2
90	CH_2CH_2CN	513.4
91	$CH_2CH_2N_3$	529.2
92		571.2

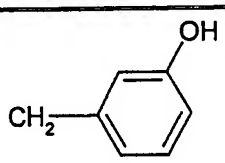
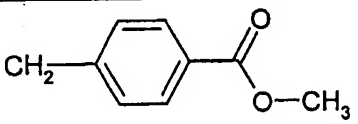
	R^4	MS: $[M+H]^+$
93		572.2
94		546.3
95		608.3
96		609.3
97		557.3
98		560.3
99		572.2
100	$CH_2CH_2CH_2NH_2$	517.3
101	$CH_2CH_2N(CH_2CH_3)_2$	559.3
102		573.2

	R^4	MS: $[M+H]^+$
103		557.3
104	$CH_2CH_2CH_2CH_2OH$	532.3
105		530.2
106		536.9 $[M+Na]^+$
107		532.3
108		594.3
109		536.2
110		534.3
111		548.1
112		576.3
113	$CH_2CH_2OCH_3$	518.2
114	$CH_2CH_2OCH_2CH_3$	532.3
115	$CH_2CH_2OCH_2CH_2OCH_3$	562.3
116	$CH_2CH_2OCH_2CH_2OCH_2CH_3$	576.3

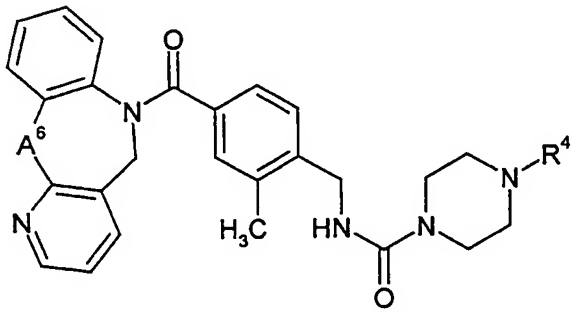
	R^4	MS: $[M+H]^+$
117		594.3
130		605.7

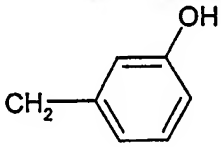
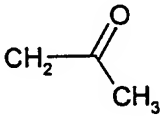
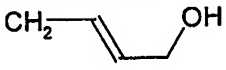
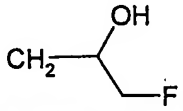
Examples 118 - 120



	A^8	R^4	MS: $[M+H]^+$
118	CH		550.3
119	CH		592.3
120	N	CH_2CH_2OH	489.0

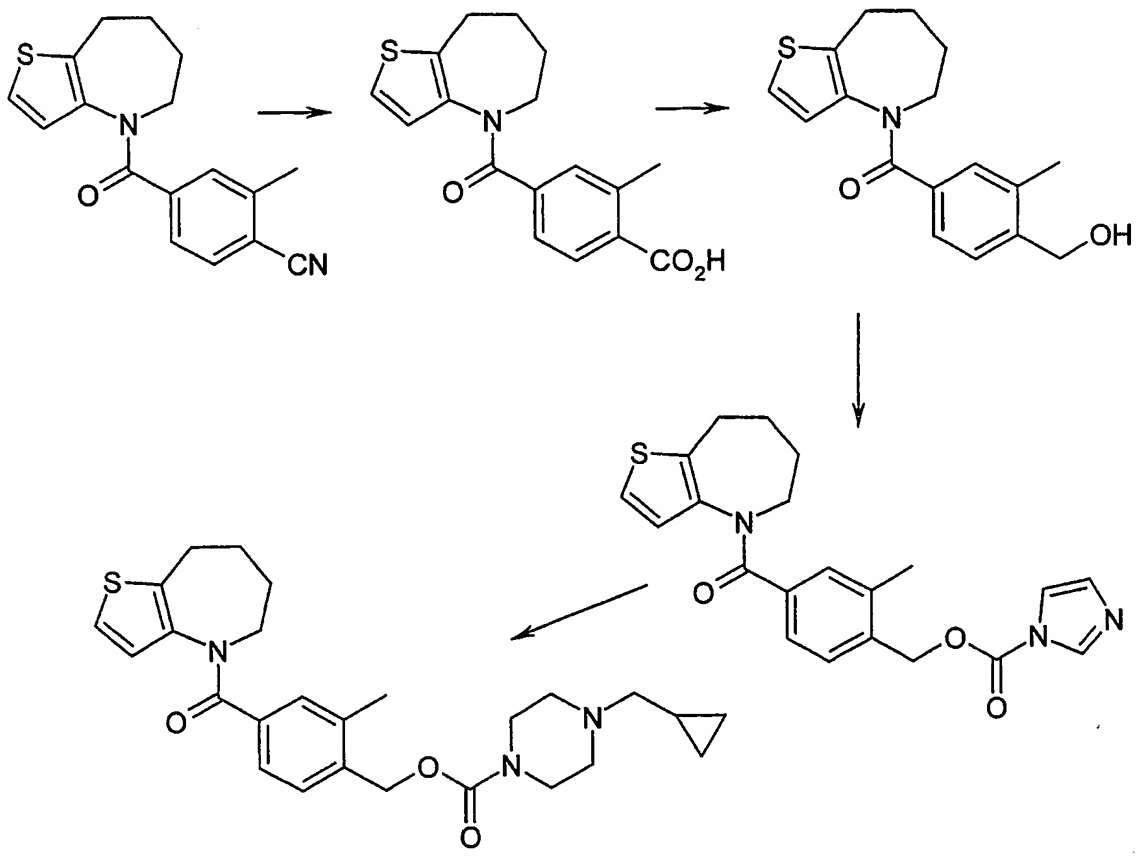
Examples 121 - 128



	A^6	R^4	MS: $[M+H]^+$
121	NH		584.9 $[M+Na]^+$
122	NH		513.3
123	NH	$CH_2CH_2CH_2NH_2$	514.3
124	NH	$CH_2CH_2NH_2$	500.3
125	O	CH_2CH_2OH	502.1
126	NH	CH_2CH_2OH	501.3
127	NH		
128	NH		533.3

Example 129

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 2-methyl-4-(5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carbonyl)-benzyl ester



4-(4-Carboxy-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

A suspension of 4-(4-cyano-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1g, 3.3mmol) in conc. sulphuric acid/water (1:1, 30ml) was heated at reflux for 5hr. The resulting solution was cooled to RT, diluted with water (20ml) and extracted with chloroform (3 × 20ml). The combined organic phases were extracted with sat. $NaHCO_3$ (2 × 20ml). The combined aqueous extracts were acidified with 1M $KHSO_4$ and extracted with chloroform (3 × 20ml). These chloroform extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a pale brown solid identified as 4-(4-carboxy-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine. (225mg, 23%).

4-(4-Hydroxymethyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

Isobutyl chloroformate (250μl, 2mmol) was added to a solution of 4-(4-carboxy-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (470mg, 1.48mmol) and *N*-methylmorpholine (230μl, 2.1mmol) in THF (15ml) at 0°C and the mixture was stirred for

1hr. The resultant suspension was filtered and the filtrate was added to a solution of sodium borohydride (131mg, 3.45mmol) in water (15ml) at 0°C. The solution was stirred at RT for 2hr, then sat. NH_4Cl (5ml) was added and the THF was removed *in vacuo*. The remaining solution was diluted with water and extracted with chloroform (3 x 20ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a pale brown solid identified as 4-(4-hydroxymethyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (330mg, 74%).

4-(4-(1-Imidazolecarbonyloxymethyl)-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine

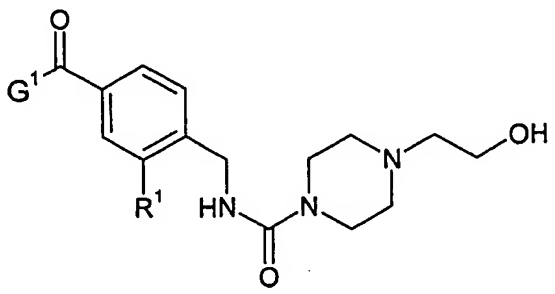
1,1'-Carbonyldiimidazole (36mg, 0.22mmol) was added to a solution of 4-(4-hydroxymethyl-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (60mg, 0.17mmol) in DMF (2ml) under nitrogen gas and the solution was stirred at RT for 18hr. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant 97% chloroform/3% methanol) to give a colourless gum identified as 4-(4-(1-imidazolecarbonyloxymethyl)-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (60mg, 45%).

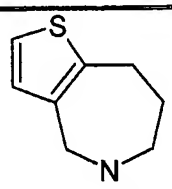
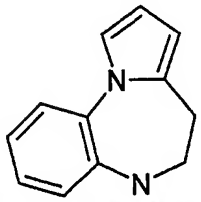
4-Cyclopropylmethyl-piperazine-1-carboxylic acid 2-methyl-4-(5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carbonyl)-benzyl ester

A mixture of 4-(4-(1-imidazolecarbonyloxymethyl)-3-methylbenzoyl)-5,6,7,8-tetrahydrothieno[3,2-b]azepine (1.0eq), 1-cyclopropylmethyl-piperazine (1.0eq) and DIEA (1.05eg) was heated at reflux for 48h. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel (eluant methanol/chloroform).

MS: $[M+H]^+ = 468$

Examples 131-132

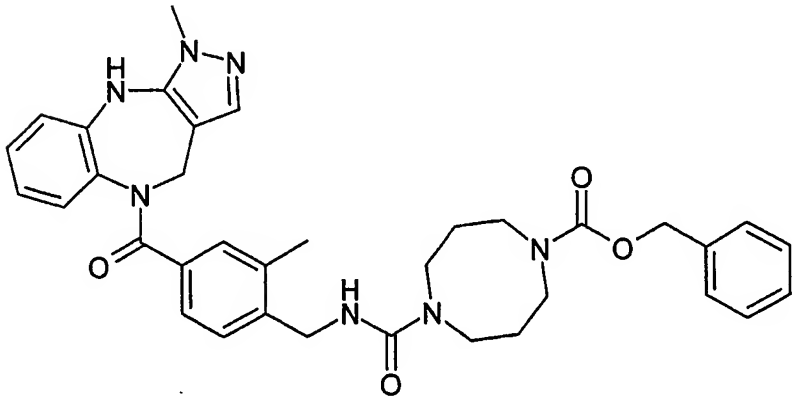


	G^1	R^1	MS: $[M+H]^+$
131		Cl	477.6
132		Me	488.7

Examples 133 and 134

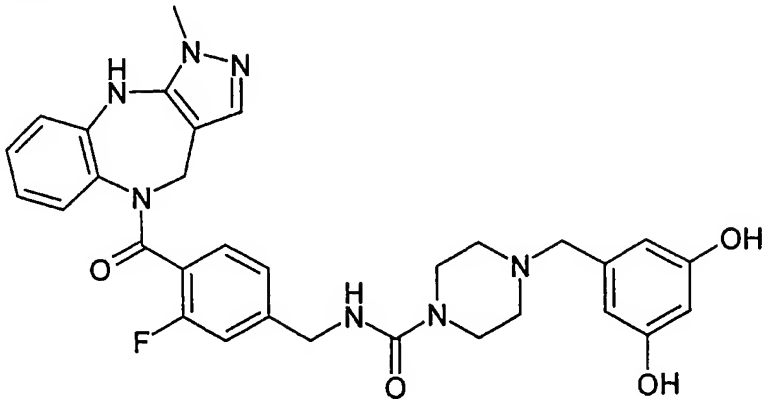
Prepared by analogous methods.

Example 133



MS: $[M+H]^+$ = 622.7

Example 134



MS: $[M+H]^+ = 586.2$

Example 135

***In vitro* Testing**

Compounds were assayed to determine their ability to mimic the cellular consequences of OT stimulation on intact cells. In the assay, the compounds of the invention cause significant cellular activation at concentrations of 30μM or less. Preferred compounds cause significant activation at concentrations of 300nM or less and can induce the same maximal effect as OT. The preferred compounds are either significantly less active or completely devoid of activity in assays for vasopressin-like activity.

Example 136

***In vivo* Testing**

Representative compounds were tested for activity in the rat uterine contractility model, which is a recognised test for OT agonism. The compounds increased the strength and frequency of the uterine contractions at doses below 50mg/kg. Selected compounds were then given either *i.c.v.* or *i.v.* to male rats and the erectile response was determined.

Example 137

Tablet for Oral Administration

Tablets containing 100mg of the compound of Example 11 as the active agent are prepared from the following:

Compound of Example 11	200.0g
Corn starch	71.0g
Hydroxypropylcellulose	18.0g
Carboxymethylcellulose calcium	13.0g
Magnesium stearate	3.0g
Lactose	195.0g
Total	*500.0g*

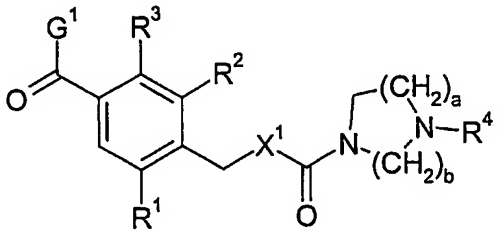
The materials are blended and then pressed to give 2000 tablets of 250mg, each containing 100mg of the compound of Example 11.

The foregoing demonstrates that the compounds according to the present invention act as agonists at the oxytocin receptor and accordingly they may find utility as pharmaceutical agents for the treatment of conditions such as sexual disorders including male erectile dysfunction, ejaculatory disorders and female sexual dysfunction, cancer of the prostate, breast, ovary and bones, osteoporosis, benign prostatic hyperplasia, post-partum bleeding, and depression. The compounds may also be used to induce labour or delivery of the placenta, to decrease arterial blood pressure, to decrease exaggerated responses to stress and to increase the nociceptive threshold.

The scope of the present invention is further defined in the following claims.

CLAIMS

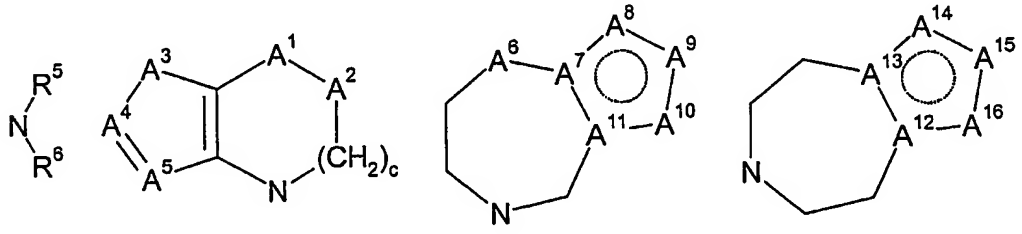
1. A compound according to general formula 1, or a pharmaceutically acceptable salt thereof



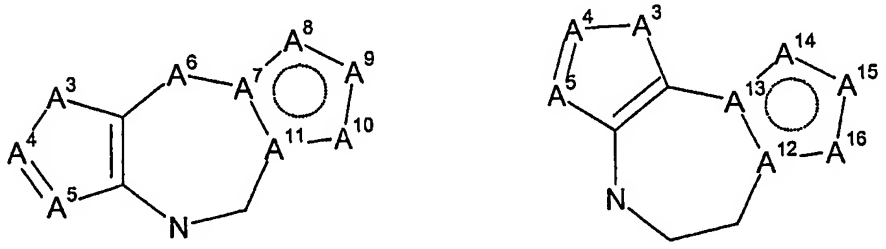
1

wherein:

G^1 is selected from a group according to general formula **2**, a group according to general formula **3**, a group according to general formula **4**, a group according to general formula **5**, a group according to general formula **6** and a group according to general formula **7**;



2 3 4 5



6 7

A^1 is selected from CH_2, CH(OH), NH, N–alkyl, O and S;

A^2 is selected from CH_2, CH(OH), C(=O) and NH;

A^3 is selected from S, NH, N–alkyl, –CH=CH– and –CH=N–;

A^4 and A^5 are each selected from CH and N;

A^6 is selected from CH_2, NH, N–alkyl and O;

A^7 and A^{11} are selected from C and N;

A^8 and A^9 are selected from CH, N, NH, $N(CH_2)_dR^7$ and S;

A^{10} is selected from –CH=CH–, CH, N, NH, $N(CH_2)_dR^7$ and S;

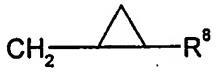
A^{12} and A^{13} are selected from N and C;

A^{14}, A^{15} and A^{16} are selected from NH, N–CH_3, S, N and CH;

X^1 is selected from O and NH;

R^1, R^2 and R^3 are each selected from H, alkyl, O–alkyl, F, Cl and Br;

R^4 is selected from H, alkyl, alkenyl, alkynyl, optionally substituted phenyl, optionally substituted thienyl, optionally substituted furyl, optionally substituted pyridyl, -(CO)-O–$(CH_2)_eR^8$, –$(CH_2)_eR^8$, -CH_2-CH=CH-CH_2-R^8, -CH_2-C≡C-CH_2-R^8, -$(CH_2)_g$-CH(OH)-$(CH_2)_h$-R^8,

-$(CH_2)_i$-O-$(CH_2)_j$-R^8 and  ;

R^5 and R^6 are independently selected from alkyl, Ar and –$(CH_2)_f$–Ar;

R^7 is selected from H, alkyl, optionally substituted phenyl, F, OH, O–alkyl, O-acyl, S-alkyl, NH_2, NH–alkyl, N(alkyl)$_2$, NH-acyl, N(alkyl)-acyl, CO_2H, CO_2–alkyl, $CONH_2$, CONH–alkyl, CON(alkyl)$_2$, CN, CF_3, optionally substituted pyridyl, optionally substituted thienyl and optionally substituted furyl;

R^8 is selected from H, alkyl, alkenyl, alkynyl, acyl, optionally substituted phenyl,

optionally substituted pyridyl, optionally substituted thienyl, optionally substituted furyl, optionally substituted pyrollyl, optionally substituted pyrazolyl, optionally substituted imidazolyl, optionally substituted oxazolyl, optionally substituted isoxazolyl, optionally substituted thiazolyl, optionally substituted isothiazolyl, F, OH, hydroxyalkyl, O–alkyl, O-acyl, S-alkyl, NH_2, NH–alkyl, $N(alkyl)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, NH-acyl, N(alkyl)-acyl, N_3, CO_2H, CO_2–alkyl, $CONH_2$, CONH–alkyl, $CON(alkyl)_2$, CN and CF_3;

Ar is selected from optionally substituted thienyl and optionally substituted phenyl;

a is 1 or 2, b is 1, 2 or 3; c is 1 or 2, d is 1, 2 or 3; e is 1, 2, 3 or 4; f is 1, 2 or 3 and g, h, i and j are all independently 1 or 2;

provided that:

not more than one of A^8, A^9 and A^{10} is NH, $N(CH_2)_dR^7$ or S;

A^7 and A^{11} are not both simultaneously N;

neither A^7 nor A^{11} is N if one of A^8, A^9 and A^{10} is NH, $N(CH_2)_dR^7$ or S;

if A^{10} is –CH=CH– then A^8 is N, A^9 is CH and both A^7 and A^{11} are C;

if A^{10} is not –CH=CH– then one of A^8, A^9 and A^{10} is NH, $N(CH_2)_dR^7$ or S or one of A^7 and A^{11} is N;

not more than one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S;

A^{12} and A^{13} are not both simultaneously N;

if one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S then A^{12} and A^{13} are both C; and

one of A^{14}, A^{15} and A^{16} is NH, N–CH_3 or S or one of A^{12} and A^{13} is N.

2 A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1, R^2 and R^3 is H and at least one is not H.

3 A compound according to Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein one of R^1, R^2 and R^3 is selected from an alkyl group, F, Cl and Br and the others are H.

4 A compound according to any preceding Claim, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from a methyl group and Cl, and R^2 and R^3 are H.

5 A compound according to any preceding Claim, or a pharmaceutically acceptable salt thereof, wherein X^1 is NH.

6 A compound according to any preceding Claim, or a pharmaceutically acceptable salt thereof, wherein a is 1 and b is 2.

7 A compound according to any preceding Claim, or a pharmaceutically acceptable salt thereof, wherein G^1 is a group according to general formula **3**.

8 A compound according to Claim 7, or a pharmaceutically acceptable salt thereof, wherein c is 2.

9 A compound according to Claim 7 or 8, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH_2 and A^2 is NH.

10 A compound according to Claim 7 or 8, or a pharmaceutically acceptable salt thereof, wherein A^1 is NH or N-alkyl and A^2 is C(=O).

11 A compound according to any of Claims 7 to 10, or a pharmaceutically acceptable salt thereof, wherein A^3 is S and A^4 and A^5 are both CH.

12 A compound according to any of Claims 7 to 10, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=CH- and A^4 and A^5 are both CH.

13 A compound according to any of Claims 7 to 10, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=N- and A^4 and A^5 are both CH.

14 A compound according to any of Claims 7 to 10, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=CH-, A^4 is CH and A^5 is N.

15 A compound according to any of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein G^1 is a group according to general formula **6** or **7**

16 A compound according to Claim 15, or a pharmaceutically acceptable salt thereof, wherein A^3 is S and A^4 and A^5 are both CH.

17 A compound according to Claim 15, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=CH- and A^4 and A^5 are both CH.

18 A compound according to Claim 15, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=N- and A^4 and A^5 are both CH.

19 A compound according to Claim 15, or a pharmaceutically acceptable salt thereof, wherein A^3 is –CH=CH-, A^4 is CH and A^5 is N.

20 A compound according to any of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein G^1 is a group according to general formula **4** or **6**

21 A compound according to Claim 20, or a pharmaceutically acceptable salt thereof, wherein A^8 is NH.

22 A compound according to Claim 20 or 21, or a pharmaceutically acceptable salt thereof, wherein A^8 is NH or N-$(CH_2)_d$-R^7.

23 A compound according to Claim 22, or a pharmaceutically acceptable salt thereof, wherein A^9 is N and A^{10} is CH.

24 A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or Cl, R^2 and R^3 are both H and X^1 is NH.

25 A compound according to Claim 1 or 24, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or Cl, R^2 and R^3 are both H, X^1 is NH, a is 1 and b is 2.

26 A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein G^1 is a group according to general formula **6**, A^4, A^5 and A^{10} are all CH, A^6 is NH, A^7 and A^{11} are both C, A^8 is N-$(CH_2)_d$-R^7 and A^9 is N.

27 A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or Cl, R^2 and R^3 are both H, X^1 is NH, a is 1, b is 2, G^1 is a group according to general formula **6**, A^4, A^5 and A^{10} are all CH, A^6 is NH, A^7 and A^{11} are both C, A^8 is N-$(CH_2)_d$-R^7 and A^9 is N.

28 A compound according to Claim 1 selected from

5-(4-(4-cyclopropylmethylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-benzylpiperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(3-hydroxybenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(3-hydroxymethylbenzyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

1-methyl-5-(3-methyl-4-(4-(4-picolyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

1-methyl-5-(3-methyl-4-(4-(3-(methylthio)propyl)piperazine-1-carbonylaminomethyl)benzoyl)-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(2-aminoethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[5,4-*b*][1,5]benzodiazepine,

5-(4-(4-(2-hydroxyethyl)piperazine-1-carbonylaminomethyl)-3-methylbenzoyl)-1-methyl-4,10-dihydropyrazolo[4,5-*c*]pyrido[2,3-*b*][1,4]diazepine,

and pharmaceutically acceptable salts thereof.

29 At least one optical isomer of a compound or salt according to any previous claim.

30 A pharmaceutical composition which comprises a compound, salt or isomer according to any of Claims 1 to 29 as an active agent

31 A pharmaceutical composition according to Claim 30 which is a tablet or capsule for oral administration.

32 A pharmaceutical composition according to Claim 30 or 31 which is for the treatment of male erectile dysfunction.

33 A use for a compound, salt or isomer according to any of Claims 1 to 29, which is as a component in the manufacture of a pharmaceutical composition.

34 A use according to Claim 33 wherein the pharmaceutical composition is to be used in the treatment of male erectile dysfunction.

35 A method of treating male or female sexual disorders which comprises the administration to a person in need of such treatment of an effective amount of a compound, salt or isomer according to any of Claims 1 to 29.

INTERNATIONAL SEARCH REPORT

Int ›nal Application No
PCT/GB 02/03593

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 C07D487/04 A61K31/495 A61P15/10 A61P15/04
//(C07D495/04,333:00,223:00),(C07D487/04,243:00,231:00),
(C07D487/04,243:00,209:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 968 938 A (P. D. WILLIAMS ET AL.) 19 October 1999 (1999-10-19) claims 1-12	1-35
A	GB 2 326 639 A (MERCK & CO., INC.) 30 December 1998 (1998-12-30) claims 1-14	1-35
A	WO 94 01113 A (OTSUKA PHARMACEUTICAL CO., LTD.) 20 January 1994 (1994-01-20) claims 1-46	1-35
A	EP 0 987 264 A (YAMANOUCHI PHARMACEUTICAL CO., LTD.) 22 March 2000 (2000-03-22) claims 1-6	1-35

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2002	05/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 02/03593

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 04, 30 April 1999 (1999-04-30) & JP 11 001456 A (OTSUKA PHARMACEUTICAL CO., LTD.), 6 January 1999 (1999-01-06) abstract -----	1-35

International Application No. PCT/GB 02 /03593

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim : 7

2. Claim : 7

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/GB 02/03593

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 02/03593

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		EP 0987264 A1	22-03-2000
		US 6340678 B1	22-01-2002
		WO 9839325 A1	11-09-1998
JP 11001456 A	06-01-1999	NONE	

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